

708+709

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
25 April 2002 (25.04.2002)

PCT

(10) International Publication Number  
WO 02/32305 A1(51) International Patent Classification<sup>7</sup>: A61B 5/0488,  
5/0476

(21) International Application Number: PCT/IB01/01932

(22) International Filing Date: 12 October 2001 (12.10.2001)

(25) Filing Language: English

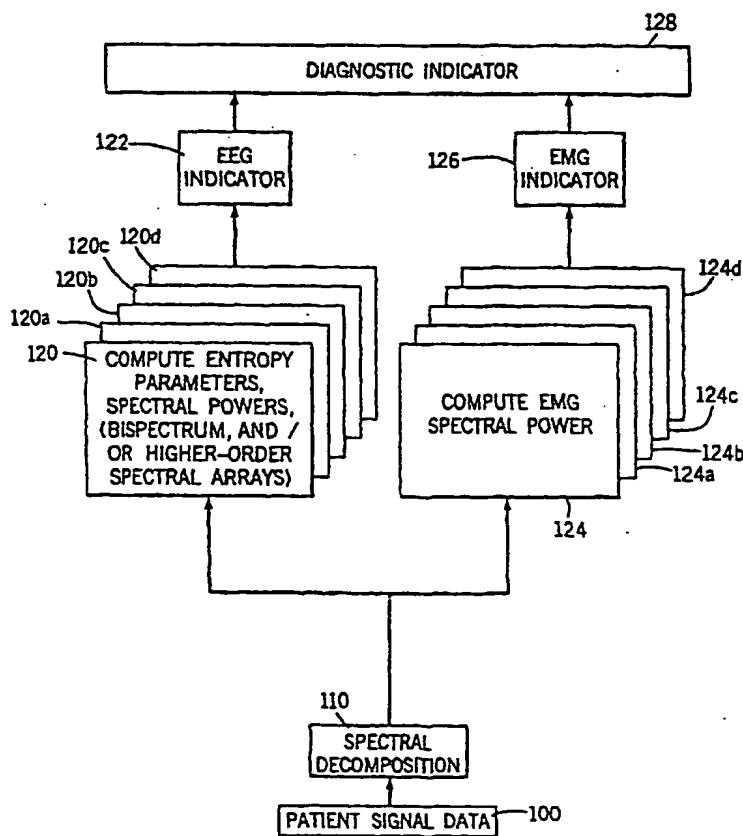
(26) Publication Language: English

(30) Priority Data:  
09/688,891 16 October 2000 (16.10.2000) US(71) Applicant: INSTRUMENTARIUM CORPORATION  
[FI/FI]; Kuortaneenkatu 2, FIN-00510 Helsinki (FI).(72) Inventors: VIERTO-OJA, Hanna, E.; Nittylaakso 30,  
FIN-02760 Espoo (FI). RANTALA, Borje, T.; Kivimaen-  
tie 56 B, FIN-00670 Helsinki (FI).(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,  
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,  
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,  
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,  
TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,  
TG).

Published:

— with international search report

(Continued on next page)

(54) Title: METHOD AND APPARATUS FOR DETERMINING THE CEREBRAL STATE OF A PATIENT WITH FAST RE-  
SPONSE

(57) Abstract: A method and apparatus for ascertaining the cerebral state of a patient. The method/apparatus may find use in ascertaining the depth of anesthesia of the patient. In one embodiment, the entropy of the patient's EEG signal data is determined as an indication of the cerebral state. A frequency domain power spectrum quantity is obtained from the patient's EMG signal data. The latter quantity can be updated more frequently than the EEG entropy due to its higher frequency. The EEG entropy indication and the EMG power spectrum indication can be combined into a composite indicator that provides an immediate indication of changes in the cerebral state of the patient. In another embodiment, the frequency range over which the entropy of the biopotential signal from the patient is determined is broadened to encompass both EEG signal data and EMG signal data and the entropy so determined used as an indication of the patient's cerebral state.

WO 02/32305 A1



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

# METHOD AND APPARATUS FOR DETERMINING THE CEREBRAL STATE OF A PATIENT WITH FAST RESPONSE

## BACKGROUND OF THE INVENTION

5           The present invention relates to a method and apparatus for determining the cerebral state of a patient. One application of the method and apparatus is determining the extent of a hypnotic state of the patient resulting, for example, from the administration of an anesthetic agent. That extent is often termed the "depth of anesthesia." In the method and apparatus of the present invention, changes in the  
10           cerebral state can be accurately and quickly determined.

          In a simplistic definition, anesthesia is an artificially induced state of partial or total loss of sensation or pain, i.e. analgesia. For most medical procedures the loss of sensation is accompanied by a loss of consciousness on the part of a patient so that the patient is amnesic and is not aware of the procedure.

15           The "depth of anesthesia" generally describes the extent to which consciousness is lost following administration of an anesthetic agent. As the magnitude of anesthetization, or depth of anesthesia, increases, an anesthetized patient typically fails to successively respond to spoken commands, loses the eyelid reflex, loses other reflexes, undergoes depression of vital signs, and the like.

20           While loss of consciousness (hypnosis, amnesia) and the loss of sensation (analgesia) are significant features of anesthesia, it should be noted that balanced high quality anesthesia must also consider muscle relaxation, suppression of the autonomous nervous system, and blockade of the neuro muscular junction. Sufficient muscle relaxation is required to ensure optimal operating conditions for the surgeon  
25           manipulating the patient's tissue. The autonomous nervous system, if not suppressed, causes the patient to respond to surgical activity with a shock reaction that effects heavily on hemodynamics and the endocrine system. To keep the patient completely motionless, the neuro muscular junctions transmitting orders from the brain to the muscles of the body need to be blocked so that the body of the patient becomes  
30           completely paralyzed.

          While the need to determine the state of all five components of anesthesia is widely recognized, ascertaining and quantifying the state of hypnosis or depth of

anesthesia in a reliable, accurate, and quick manner has been, and is, the subject of extensive attention. One reason for this is its importance. If the anesthesia is not sufficiently deep, the patient may maintain or gain consciousness during a surgery, or other medical procedure, resulting in an extremely traumatic experience for the patient, anesthesiologist, and surgeon. On the other hand, excessively deep anesthesia reflects an unnecessary consumption of anesthetic agents, most of which are expensive. Anesthesia that is too deep requires increased medical supervision during the surgery recovery process and prolongs the period required for the patient to become completely free of the effects of the anesthetic agent. A second reason for the continuing study and attention being given to monitoring the hypnotic condition of a patient arises because of its difficulty: that is, anesthetic agents alter the activity and state of the patient's brain and these changes are not always easy to detect.

A measure of the depth of anesthesia that may be used for research purposes is found in an Observer's Assessment of Alertness and Sedation or OAAS. The OAAS determines the level of consciousness or, conversely, the depth of sedation or anesthesia, based on a patient's response to external stimuli. One such assessment that classifies the depth of anesthesia in six levels, is summarized by the table below. The transition from consciousness to unconsciousness may be deemed to occur when the OAAS score changes from level 3 to level 2. Level zero corresponds to a state of deep anesthesia in which the patient shows no response to a very painful stimulus.

OAAS Score	Distinctive Characteristics
5	Patient replies readily to spoken commands, eyes open, awake.
4	Patient is sedated, but replies to spoken commands, mild ptosis.
3	Patient ceases to reply to loud commands, eye lid reflex present.
2	Patient does not reply to spoken commands, no eye lid reflex.
1	Patient does not react to TOF stimulation (50 mA) with movement.
0	Patient does not react to tetanic stimulation with movement.

"Ptosis" is a drooping of the upper eyelids. "TOF stimulation" ("train-of-four") is a very short, painful electrical (50 mA) stimulus applied to the ulnar nerve in the arm of the patient, repeated four times to evaluate the intensity of muscular

contraction. In "tetanic stimulation" the electrical current (50 mA) is applied continuously for a period of time, such as 5 seconds. The ulnar nerve is the nerve which, when pinched, gives rise to the well known "crazy or funny bone" effect.

While useful for research and other purposes, an OAAS scale provides only a limited number of scaling levels and is limited in practical use because of the attention required from the anesthesiologist and the use of painful stimuli.

It has long been known that the neurological activity of the brain is reflected in biopotentials available on the surface of the brain and on the scalp. Thus, efforts to quantify the extent of anesthesia induced hypnosis have turned to a study of these biopotentials. The biopotential electrical signals are usually obtained by a pair, or plurality of pairs, of electrodes placed on the patient's scalp at locations designated by a recognized protocol and a set, or a plurality of sets or channels, of electrical signals are obtained from the electrodes. These signals are amplified and filtered. The recorded signals comprise an electroencephalogram or EEG.

Among the purposes of filtering is to remove electromyographic (EMG) signals from the EEG signal. EMG signals result from muscle activity of the patient and will appear in electroencephalographic electrodes applied to the forehead or scalp of the patient. They are usually considered artifacts with respect to the EEG signals. Since EMG signals characteristically have most of their energy in a frequency range (40 - 300 Hz) which is different than that of the EEG, major portions of the EMG signals can be separated from the EEG signal.

A typical EEG is shown in Fig.1. A macro characteristic of EEG signal patterns is the existence of broadly defined low frequency rhythms or waves occurring in certain frequency bands. Four such bands are recognized: Delta (0.5 - 3.5 Hz), Theta (3.5 - 7.0 Hz), Alpha (7.0 - 13.0 Hz) and Beta (13.0 - 32.0 Hz). Alpha waves are found during periods of wakefulness and may disappear entirely during sleep. The higher frequency Beta waves are recorded during periods of intense activation of the central nervous system. The lower frequency Theta and Delta waves reflect drowsiness and periods of deep sleep.

By analogy to the depth of sleep, it can be said that the frequency of the EEG will decrease as the depth of anesthesia increases, while the magnitude of the

signal initially often increases. However, this gross characterization is too imprecise and unreliable to use as an indication of such a critical medical aspect as the extent of hypnosis. Further, EEG signal changes during anesthesia may not fully correlate with changes in the hypnotic state of the patient. For example, it has been reported that in a  
5 12-18 Hz frequency band, EEG activity initially increases as anesthetic agents are administered and only thereafter decreases as anesthesia deepens.

The foregoing circumstance has led to the investigation and use of other techniques to study EEG waveforms to ascertain the underlying condition of the brain, including the depth of anesthesia to which a patient is subjected. It will be immediately  
10 appreciated from Fig. 1 that EEG signals are highly random in nature. Unlike other biopotential signals, such as those of an electrocardiogram (ECG), an EEG normally has no obvious repetitive patterns, the morphology and timing of which can be conveniently compared and analyzed. Nor does the shape of the EEG waveform correlate well to specific underlying events in the brain. Hence, except for certain phenomena, such as  
15 epileptic seizures, which are readily apparent from visual inspection of an EEG, the indication of other conditions in the brain in the EEG is much more subtle.

Prefatory to the use of other techniques, the EEG signals are subjected to analog to digital signal conversion by sequentially sampling the magnitude of the analog EEG signals and converting same to a series of digital data values. The sampling is  
20 typically carried out at a rate of 100 Hz or greater. The digital signals are stored in the magnetic or other storage medium of a computer and then subjected to further processing to ascertain the underlying state of the brain. Such processing typically uses sets of sequential EEG signal samples or data points representing a finite block of time, commonly termed an "epoch." The analysis of the data is usually carried out on a  
25 moving average basis employing a given epoch and a certain number of backward epochs.

Some of the techniques by which EEG signals can be analyzed in an effort to determine the depth of anesthesia are well described in Ira J. Rampil, *A Primer for EEG Signal Processing in Anesthesia*, Vol. 89, Anesthesiology No. 4, pgs. 980 et seq.,  
30 October 1998.

One such technique is to examine, in some meaningful way, how the

voltage of an EEG signal changes over time. Such an analysis is termed a "time-domain analysis." Because of its generally random nature, an EEG signal is not a deterministic signal. This means that it is not possible to exactly predict future values of the EEG from past values in the manner that, for example, the shapes of past QRS complexes in an ECG signal can be used to predict future values for analytical and diagnostic purposes. However, certain statistical characteristics of random signals, such as an EEG, can be determined and used for analytic purposes.

Time-domain based EEG analysis methods have not proven greatly successful in clinical applications since the results do not behave in a completely consistent manner. However, such methods have been reported in the use of an electrical power parameter derived from the time-domain EEG signal voltage to control administration of an anesthetic agent. Combinations of time-domain based statistic parameters have been used to analyze EEG data. Efforts have also been made to use the number of times the EEG signal crosses the zero voltage level in a given period to analyze EEG signal data.

Time-domain based analysis is however useful in the study and quantification of burst suppression in the EEG. During deep sleep or anesthesia, the EEG time-domain signal may develop a pattern of activity which is characterized by alternating periods or "bursts" of normal, or high frequency and amplitude, voltage signals and periods of low or no voltage, which periods are termed those of "suppression." The extent of this phenomenon can be expressed as a "burst suppression ratio (BSR)" which is a time domain EEG parameter describing the time the EEG voltage is in the suppressed state as a fraction of the sampling period.

A second approach to analyzing EEG waveforms examines signal activity as a function of frequency, i.e. a "frequency-domain analysis." It has long been recognized that complex waveforms, such as EEG signals, can be decomposed, or transformed, into a plurality, or spectrum, of simple sine or cosine waves of various frequencies, amplitudes, and phases. Frequency-domain spectra can be obtained from sequential time-domain EEG signal data by a Fourier transform. Frequency-domain analysis analyzes the spectrum of frequency signals obtained from the transform to determine characteristics and features occurring in wave forms having the various

frequencies of the spectrum. The results of an EEG frequency-domain analysis are typically graphically displayed as a power versus frequency histogram in which frequency is graphed on the abscissa and power is graphed on the ordinate.

Further efforts to obtain useful information from electroencephalograms have employed higher order analyses, including the bispectrum and trispectrum. The bispectrum, which measures the correlation of phase between two different frequency components and quantifies the relationships among the underlying sinusoidal components of the EEG, has received considerable attention. The bispectrum specifically quantifies the relationship between sinusoids at two primary frequencies  $f_1$  and  $f_2$  and a modulation component at the frequency  $f_1 + f_2$ . A strong phase relationship between  $f_1$ ,  $f_2$  and  $f_1 + f_2$  creates a large bispectral value for frequency  $f_1 + f_2$ . However, because the calculation must be performed using complex number arithmetic for several thousand  $f_1$ ,  $f_2$ , and  $f_1 + f_2$  frequency combinations, the computations to obtain bispectral information are rather arduous.

For clinical use, it is desirable to simplify the results of EEG signal analysis of the foregoing, and other types, into a workable parameter that can be used by an anesthesiologist in a clinical setting when attending the patient. Ideally, what is desired is a simple, single parameter or index that quantifies the depth of anesthesia on a consistent, continuous scale extending from full alertness to maximally deep, but reversible, hypnosis. To be fully useful such a scale should maintain its consistency, notwithstanding the differing pharmacological effects of different anesthetic agents, as well as the differing physiologies of different patients.

Various such parameters for relating EEG signal data to the hypnotic state of the patient are discussed in the literature. Several use frequency domain power spectral analysis. These parameters include peak power frequency (PPF), median power frequency (MPF), and spectral edge frequency (SEF). A peak power frequency (PPF) parameter uses the frequency in a spectrum at which occurs the highest power in the sampled data as an indication of the depth of anesthesia. The median power frequency (MPF) parameter, as its name implies, uses the frequency that bisects the spectrum. In the same fashion, the spectral edge frequency uses the highest frequency in the EEG signal. A modification of the latter is the SEF 95 parameter, which is the frequency



below which 95% of the power in the spectrum resides.

To improve the consistency of an indicator of the hypnotic state or depth of anesthesia, several parameters are often employed in combination. For example, the spectral edge frequency (SEF) parameter may be combined with the time-domain burst suppression ratio (BSR) parameter to improve the consistency and accuracy with which the depth of anesthesia can be indicated.

While parameters of the foregoing types can detect changes in the EEG caused by anesthetic agents and hence are useful in determining the depth of anesthesia, they suffer from an inability to be calibrated to behavioral endpoints and because of their sensitivity to the different EEG patterns induced by different anesthetic agents.

More complex combinations of parameters are described in U.S. Patents 4,907,597; 5,010,891; 5,320,109; and 5,458,117 to Nassib Chamoun or Chamoun et al. and are employed in the anesthesia monitor product made and sold by the assignee of the patents, Aspect Medical Systems of Framingham, MA. The patents describe various combinations of a time-domain subparameter and frequency-domain subparameters, including a high order spectral subparameter, to form a single variable, termed the bispectral index (BIS), that correlates behavioral assessments of sedation and hypnosis over a range of anesthesia for several anesthetic agents. Because of this ability, the Aspect Medical Systems product has found clinical acceptance.

The bispectral index, BIS, consists of the following three subcomponents: SyncFastSlow, BetaRatio, and Burst Suppression. The calculation of the subparameter SyncFastSlow utilizes bispectral analysis in the frequency-domain. The SyncFastSlow parameter corresponds to the logarithm of the ratio of the sum of all bispectral peaks in the frequency range 0.5 - 47 Hz divided by the sum in the range 40 - 47 Hz. The bispectral information in the SyncFastSlow subparameter does not, by itself, give sufficient information over the range of hypnosis thus requiring combination with the other subparameters. The BetaRatio subparameter gives the logarithm of the power ratio in the frequency ranges 30 - 47 Hz and 11 - 20 Hz. It is a frequency-domain parameter that has been found to work best in light sedation. As noted above, in very deep levels of anesthesia, EEG signal contains data samples in which the EEG activity is suppressed. The Burst Suppression Ratio obtained from a time-domain analysis of the

EEG signal describes the relative content of burst and suppression in the signal. The Burst Suppression Ratio is operative in deep anesthesia in which the suppression occurs.

5 The resulting bispectral index, BIS, is a combination of these three subparameters. The combining algorithm weights the different subparameters according to their range of best performance. While the details of the algorithm are unpublished and proprietary, it is known that different subparameters or combination of subparameters are employed depending on the level of hypnosis or depth of anesthesia. For example, light sedation, it is necessary to use the bispectral SyncFastSlow subparameter in conjunction with the BetaRatio subparameter in order produce reliable results. For deep anesthesia it is necessary to combine the bispectral subparameter SyncFastSlow with the Burst Suppression Ratio subparameter to produce reliable results. The algorithm appears circuitous in that in order to make the proper combination of subparameters required to accurately determine the depth of anesthesia, the algorithm must know what the level of anesthesia is which, in turn, requires the proper subparameter combination.

15 Certain paradoxical behavior of the bispectral index (BIS) has been reported. See Detsch, et al. *"Increasing Isoflurane Concentration may cause Paradoxical Increases in the EEG bispectral index in Surgical Patients"*, Br. J. Anaesth. 84 (2000), pgs. 33-37. Because the index uses a plurality of subparameters and combinations thereof in different regions of hypnosis, this behavior may occur when the hypnotic level of a patient is at a boundary of the regions, for example, in the range between "surgical levels" and "deep hypnosis."

20 Further, computation of the bispectral index (BIS) parameter requires averaging several epochs of EEG data. Thus, this index may be not sufficiently fast to detect changes in the state of a patient as is required in the clinical situation. See, Baker, et al. *Electroencephalographic Indices Related to Hypnosis and Amnesia During Propofol Anaesthesia for Cardioversion*, Anaesthesia and Intensive Care, Vol. 28, No.4, 2000. Hence, the BIS index may indicate recovery several seconds after a patient has already opened his/her eyes. This can be a serious problem in the use of the BIS index.

25 By knowing the depth of anesthesia, the anesthesiologist can more precisely control the amount of anesthetic agent administered to a patient. Often this results in a reduction in

30

the amount of agent administered. However, the lessened amount of anesthetic agent increases the risk that the patient will awaken during surgery. It is therefore essential that an anesthesiologist knows immediately if a patient is approaching consciousness out of the hypnotic state.

5 A different approach to the analysis of electroencephalographic signals is to attempt to quantify the complexity of the highly random EEG signal for use as an indication of the depth of anesthesia. This approach is based on the premise that neuronal systems, such as those of the brain, have been shown to exhibit a variety of non-linear behaviors so that measures based on the non-linear dynamics of the EEG  
10 signal should allow direct insight into the state of the underlying brain activity.

There are a number of concepts and analytical techniques directed to the complex nature of random and unpredictable signals. One such concept is entropy. Entropy, as a physical concept, describes the state of disorder of a physical system. When used in signal analysis, entropy addresses and describes the complexity,  
15 ~~unpredictability, or randomness characteristics of a signal. In a simple example, a signal~~ in which sequential values are alternately of one fixed magnitude and then of another fixed magnitude has an entropy of zero, i.e. the signal is totally predictable. A signal in which sequential values are generated by a random number generator has greater complexity and a higher entropy.

20 Applying the concept of entropy to the brain, the premise is that when a person is awake, the mind is full of activity and hence the state of the brain is more non-linear, complex, and noise like. Since EEG signals reflect the underlying state of brain activity, this is reflected in relatively more "randomness" or "complexity" in the EEG signal data, or, conversely, in a low level of "order." As a person falls asleep or is  
25 anesthetized, the brain function begins to lessen and becomes more orderly and regular. As the activity state of the brain changes, this is reflected in the EEG signals by a relative lowering of the "randomness" or "complexity" of the EEG signal data, or conversely, increasing "order" in the signal data. When a person is awake, the EEG data signals will have higher entropy and when the person is asleep the EEG signal data  
30 will have a lower entropy.

With respect to anesthesia, an increasing body of evidence shows that EEG

signal data contains more "order", i.e. less "randomness", and lower entropy, at higher concentrations of an anesthetic agent, i.e. greater depth of anesthesia, than at lower concentrations. At a lower concentration of anesthetic agent, the EEG signal has higher entropy. This is due, presumably, to lesser levels of brain activity in the former state than in the latter state. See *"Stochastic complexity measures for physiological signal analysis"* by I.A. Rezek and S.J. Roberts in IEEE Transactions on Biomedical Engineering, Vol. 4, No. 9, September 1998 describing entropy measurement to a cut off frequency of 25 Hz and Bruhn, et al. *"Approximate Entropy as an Electroencephalographic Measure of Anesthetic Drug Effect during Desflurane Anesthesia"*, Anesthesiology, 92 (2000), pgs. 715-726 describing entropy measurement in a frequency range of 0.5 to 32 Hz. See also H. Viertiö-Oja et al. *"New method to determine depth of anesthesia from EEG measurement"* in J. Clin. Monitoring and Comp. Vol. 16 (2000) pg. 16 which reports that the transition from consciousness to unconsciousness takes place at a universal critical value of entropy which is independent of the patient.

The pertinence of the concept of entropy to the conscious and unconscious states of the brain is also supported in recent theoretical work (see Steyn-Ross et al., Phys. Rev. E60 1999, pgs. 7229-7311) which applies thermodynamic theory to the study of the brain. This work points to the conclusion that when a patient undergoing anesthetization passes from the conscious state to the unconscious state, a thermodynamic phase transition of the neural system of the brain takes place which is roughly analogous to the phase change occurring when water freezes into ice. During the process of freezing, an amount of entropy, proportional to the latent heat of the process is removed so that water and ice have different entropies. The conscious and unconscious states of the brain may therefore similarly be expected to have distinct, different values of entropy. The premise that loss of consciousness can be regarded as analogous to a thermodynamic phase transition, lends further support to the concept of entropy as a fundamental characteristic of the cerebral state of the brain and to the use of entropy in determining depth of anesthesia as employing a quantity reflecting the basic mechanisms of the brain rather than derived phenomena, such as power spectra, reflecting those mechanisms.

In sum, the following can be said. First, certain forms of entropy have generally been found to behave consistently as a function of anesthetic depth. See Bruhn et al. and H. E. Viertiö-Oja et al. "*Entropy of EEG signal is a robust index for depth of hypnosis*", *Anesthesiology* 93 (2000) A, pg. 1369. This warrants consideration of entropy as a natural and robust choice to characterize levels of hypnosis. Also, because entropy correlates with depth of anesthesia at all levels of anesthesia, it avoids the need to combine various subparameters as in the bispectral index (BIS). Second, the transition from consciousness to unconsciousness takes place at a critical level of entropy which is independent of the patient. See Viertio-Oja et al. in *J. Clin. Monitoring and Computing*. Thirdly, and of particular practical significance, recovery of a patient toward consciousness from anesthesia can often be predicted by a rise of entropy toward the critical level.

A number of techniques and associated algorithms are available for quantifying signal complexity, including those based on entropy, as described in the Rezek and Roberts article in *IEEE Transactions on Biomedical Engineering* article. One such algorithm is that which produces spectral entropy for which the entropy values are computed in frequency space. Another algorithm provides approximate entropy which is derived from the Kolmogorov-Sinai entropy formula and computed in Taken's embedding space. See Steven M. Pincus, Igor M. Gladstone, and Richard A. Ehrenkranz, "*A regularity statistic for medical data analysis*", *J. Clin. Monitoring* 7 (1991), pgs. 335-345. A program for computing approximate entropy is set out in the Bruhn et al., article in *Anesthesiology*. The spectral entropy and approximate entropy techniques have found use in analyzing the complexity of EEG signal data.

Another technique for non-linear analysis of highly random signals is expressed in Lempel-Ziv complexity in which the complexity of a string of data points is given by the number of bytes needed to make the shortest possible computer program which is able to generate the string. See Abraham Lempel and Jacob Ziv, "*On the complexity of finite sequences*", *IEEE Trans., IT-22* (1976) pgs. 75-81.

A still further approach that may be applied to EEG signal analysis is fractal spectrum analysis based on chaos theory. In fractal spectrum analysis, the EEG signal is divided into a harmonic component and a fractal component. The harmonic

component includes the simple frequencies whereas the fractal component contains the part which is invariant under scaling in time. It has been found that the fractal exponent Beta which corresponds to the frequency power law  $1/f^\beta$  increases consistently in the course of deepening anesthesia.

5

### BRIEF SUMMARY OF THE INVENTION

An object of the present invention is to provide an improved method and apparatus for accurately determining the cerebral state of a patient, including the hypnotic or consciousness state of a patient and the depth of anesthesia that a patient is experiencing.

10

A particular object of the present invention is to provide such a method/apparatus that can rapidly make such determinations, especially when a patient is emerging to the conscious state from unconsciousness.

The gist of the present invention is to combine an effective measure of the cerebral state of a patient derived from EEG signal data, preferably a complexity measurement such as spectral entropy or approximate entropy, with a more rapidly obtainable measure derived from EMG signal data and to use the combination as a cerebral state indication. When used as an indication of the hypnotic state, or depth of anesthesia, of the patient, the measure derived from the EMG signal data enhances and confirms the determination of the hypnotic state made using the EEG signal data and renders ascertaining changes in the hypnotic state of the patient more rapid. This is of particular advantage in alerting an attending anesthesiologist to the possibility that an anesthetized patient may shortly regain consciousness so that the anesthesiologist can take timely, appropriate action. The measure derived from the EMG signal data may comprise spectral power data.

20

25

30

Both the EEG and EMG signal data are typically obtained from the same set of electrodes applied, for example, to the forehead of the patient. The EEG signal component dominates the lower frequencies (up to about 30 Hz) contained in the biopotentials existing in the electrodes and EMG signal component dominates the higher frequencies (about 50 Hz and above).

The presence of EMG signal data shows that the patient is conscious and

thus can provide a rapid indication of the conscious-unconscious state of the patient. Importantly, because of the higher frequency of the EMG data signal, the sampling time can be significantly shorter than that required for the lower frequency EEG signal data. This allows the EMG data to be computed more frequently so that the overall diagnostic indicator can quickly indicate changes in the state of the patient.

In one embodiment of the invention, the EEG signal data and the EMG signal data are separately analyzed and thereafter combined into a diagnostic index or indicator. As noted above, because of the celerity with which changes in the anesthetic state of the patient can be determined from the EMG data, the overall index can quickly inform the anesthesiologist of changes in the state of the patient.

In another embodiment of the present invention, the spectral range of the complexity computations, i.e. entropy computations, is widened to extend into the EMG range. Thus, the spectral range over which the complexity computations are carried out to provide an indicator may extend from some lower frequency of, for example 0.5 to 7 Hz, up to a frequency above 32 Hz. To filter out power line interference, the spectral range may be divided into bands with the elimination of frequencies around 50, 60 Hz and 100, 120 Hz. For example, in an embodiment in which the spectral range extends to approximately 150 Hz, a lower frequency band (0.5 - 47 Hz) will contain mostly EEG signal data while two upper bands (63 - 97 Hz and 123 - 147 Hz) will include primarily EMG activity. The use of a widened frequency range does not require a division of the spectrum into two segments or does the first embodiment because all components in the widened frequency range are treated in the same manner. And, any boundary within the spectral range would be artificial since the frequency bands for the EEG and EMG signal data are overlapping. The same analytical techniques are thus used for all levels of hypnosis from conscious state down to deep anesthesia, the paradoxical behavior found with indicators employing a plurality of subparameters and rules of combination for various levels of anesthesia is avoided.

Further, the complexity measurement obtained in this second embodiment of the invention can be updated as often as is permitted by the higher frequencies of the EMG signal data in the widened spectral range of the complexity computation. This will provide a very current indication to the anesthesiologist of the depth of anesthesia of the

patient.

The indicator obtained from the signal complexity computation over the widened spectral range can be used in conjunction with a complexity measurement obtained only from the EEG portions of the frequency spectrum to provide useful information to the anesthesiologist regarding what portion of the indicator comes from cerebral activity and what portion comes from muscle activity.

Various other features, objects, and advantages of the invention will be made apparent from the following detailed description and the drawings.

## BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING

Fig 1 shows an electroencephalogram.

Figs. 2a and 2b are graphs showing values of entropy as compared to the conventional OAAS scale for a patient receiving an anesthetic agent;

Figs. 3a and 3b are graphs showing values of entropy of a patient at surgical levels of anesthesia;

Figs. 4a and 4b are graphs showing values of entropy as compared to the conventional OAAS scale for a patient emerging from anesthesia;

Figs. 5a, 5b, and 5c are comparative graphic showings of various techniques for analyzing EEG signals;

Fig. 6 is a flow chart showing one embodiment of the present invention;

Figs. 7a, 7b, and 7c are graphs showing OAAS levels, EEG entropy, and EMG amplitude, respectively;

Fig. 8 is a flow chart showing another embodiment of the present invention;

Figs. 9a, 9b, 9c, and 9d are graphs showing OAAS levels and corresponding EEG and EMG based indicators of the depth of anesthesia;

Fig. 10 is a graph showing combined EEG and EMG entropy values; and

Fig. 11 shows apparatus for carrying out the present invention.

## DETAILED DESCRIPTION OF THE INVENTION

In a preferred embodiment of the invention, relevant information with respect to depth of anesthesia is extracted from the EEG signal data by computing a



parameter that characterizes the amount of disorder or complexity in the signal. Suitable mathematical techniques include, for example, spectral entropy described in Rezek and Roberts, approximate Kolmogorov-Sinai entropy described in Pincus et al., and complexity described in Lempel-Ziv. The use of spectral entropy is deemed  
5 advantageous because of its superior computational simplicity and is described below.

Computation of the spectral entropy of a signal according to Rezek and Roberts includes four steps. The first is the power spectrum calculation. The Fourier transform  $X(f_i)$  of the signal  $x(t_i)$  is computed by the fast Fourier transform technique (FFT). The power spectrum  $P(f_i)$  is calculated by squaring the amplitudes of each  
10 element  $X(f_i)$  of the Fourier transform:

$$P(f_i) = X(f_i) \cdot X^*(f_i) \quad (1)$$

where  $X^*(f_i)$  is the complex conjugate of the Fourier component  $X(f_i)$ .

~~15 The power spectrum is then normalized. The normalized power spectrum~~  
 $P_n(f_i)$  is computed by setting a normalization constant  $C_n$  so that the sum of the normalized power spectrum over the selected frequency region  $[f_1, f_2]$  is equal to one:

$$\sum_{f_i=f_1}^{f_2} P_n(f_i) = C_n \sum_{f_i=f_1}^{f_2} P(f_i) = 1 \quad (2)$$

20 In the summation step, the unnormalized spectral entropy corresponding to the frequency range  $[f_1, f_2]$  is computed as a sum

$$S[f_1, f_2] = \sum_{f_i=f_1}^{f_2} P_n(f_i) \log\left(\frac{1}{P_n(f_i)}\right) \quad (3)$$

25 Thereafter, the entropy value is normalized. In order to normalize the entropy value to range between 1 (maximum disorder) and 0 (complete order), the value is finally divided by the factor  $\log(N[f_1, f_2])$  where  $N[f_1, f_2]$  is equal to the total number of frequency components in the range  $[f_1, f_2]$ :

$$S_N[f_1, f_2] = \frac{S[f_1, f_2]}{\log(N[f_1, f_2])} \quad (4)$$

In the original work by Rezek and Roberts, the frequency range considered was the range below  $f_2 = 25$  Hz, as it is generally assumed that most of the EEG activity is confined to the frequency band below approximately 30 Hz.

Fig. 2 shows, as a function of time, values of entropy as computed above as compared to an OAAS scale for a patient receiving an anesthetic agent.

Fig. 2a indicates the OAAS level as determined by an anesthesiologist attending the patient. As noted above, at an OAAS level 5, the patient is fully awake whereas at the OAAS level 0 corresponds to a deep state of anesthesia in which the patient shows no response to tetanic stimulation. Horizontal line 10 indicates a level at which transition from the conscious to unconscious state is deemed to take place, i.e. between OAAS level 3 and OAAS level 2.

In the example shown in Fig. 2, the attending anesthesiologist considers the patient to have moved from OAAS level 5 to OAAS level 4 at about three minutes. At about four minutes, the patient is deemed to have dropped to OAAS level 3.

Thereafter, at about four and a half minutes, the patient is deemed to have lost consciousness as by failing to respond to verbal commands and the loss of the eyelid reflex. This is evidenced in the change from level 3 to below level 2 and the crossing of horizontal line 10.

Fig. 2b shows a value of entropy computed from five seconds of data as graph 20 and a value of entropy computed as median values of twelve sequential five second epochs (sixty seconds) of data as graph 30. As can be seen from Fig. 2b, as the consciousness of the patient decreases from the commencing of monitoring, both graphs 20 and 30 similarly decrease and cross horizontal line 40 which identifies the entropy level that characterizes the transition from the conscious state to the unconscious state.

In accordance with a protocol for the OAAS in use, the anesthesiologist commences the application of TOF stimulations to determine the depth of anesthesia on the OAAS scale. In the case shown in Fig. 2, the stimulations cause the patient to regain consciousness at about eight minutes.

It will be seen from Fig. 2 that graphs 20 and 30 follow, and provide an accurate indication of, the state of consciousness of the patient, as presented on the OAAS scale.

5 Figs. 3a and 3b show the values of entropy at surgical levels of anesthesia, i.e. when the OAAS scale is zero as shown in Fig. 3a. Horizontal line 40 in Fig. 3 is the same as horizontal line 40 in Fig. 1 and comprises the entropic value forming the borderline between the conscious and unconscious states.

10 Figs. 4a and 4b shows a rapid recovery of a patient from surgical levels of anesthesia to consciousness. The rise in the values of entropy, informs the anesthesiologist of the approaching recovery to the conscious state.

While the invention has been described as using spectral entropy, Fig. 5a, 5b, and 5c illustrate an example of anesthesia induction and emergence showing the suitability of the complexity measurements of approximate entropy and Lempel-Ziv complexity as well as spectral entropy to determine the depth of anesthesia.

15 ~~Measurements made using both shorter and longer samples of signal data are shown.~~

Other techniques for analyzing the EEG signal data can also be used, if desired, such as higher order frequency domain analysis including the bispectrum and trispectrum, frequency domain power spectral analysis, and combinations of analytical quantities, such as the bispectral index (BIS).

20 Measurement of electromyographic (EMG) activity contained in the biopotentials in the electrodes on the forehead, or other region of the scalp, of the patient can provide useful information concerning the state of an anesthetized patient. As the level of anesthesia approaches inadequacy, a painful stimulus causes a contraction of the frontalis muscle (frowning) which can be detected as peaks in the EMG amplitude of the  
25 signal obtained from the electrodes applied to the forehead of the patient. EMG activity exists as long as the muscles are not paralyzed. This reaction can often be observed substantially before the pain eventually brings the patient to consciousness. EMG signal data can thus provide an early warning sign for the anesthesiologist to increase the level of anesthetics in order to prevent consciousness and awareness during surgery.

30 Further, due to the high frequency range of the primary portion of the EMG activity above 40 Hz, a comparatively small time window is sufficient for

computations using these frequency components, so that changes in the EMG activity can be detected substantially faster than changes in the EEG signal. Specifically, most of the component in the EEG signal resulting from brain activity is contained in the frequency range below 30 Hz. In order to obtain a good estimate of this activity by any mathematical procedure, the length of the signal used for computations has to be sufficient. In practice, the lowest frequency of the band sets the size for the signal length. For example, for an EEG signal band from 0.5 Hz to 32 Hz, a signal sample 60 seconds long is required to obtain at least 30 cycles for each component. This sets a lower limit to the response time for assessing changes in patient brain activity from the EEG signal data. That is, the frequency with which all components of the EEG signal data indicator can be computed and fully updated is about once every 60 seconds. By contrast, an EMG signal data in a 63 - 97 Hz band requires only 0.5 seconds of data to obtain 30 cycles. The EMG signal data can thus be fully updated every half second. Because it can be so quickly updated, the EMG signal data can therefore provide an early warning sign for the anesthesiologist to increase, for example, the level of anesthetic agent administered to the patient in order to prevent awareness during surgery.

Fig. 6 is a flow chart showing the steps for producing an improved diagnostic indication using EEG signal data and more rapidly indicative EMG signal data in accordance with one embodiment of the present invention. In step 100, the signal data corresponding to the biopotentials appearing in the electrodes placed on the scalp of the patient is obtained. In step 110, the signal data is subjected to spectral decomposition. This, may, for example, be carried out using Fourier analysis.

The spectra are then divided into those representing the low frequency portions of the measured signal, for example, less than 30 - 50 Hz and those representing the high frequency portion of the measured signal for example, those representing frequencies of 50 Hz and above.

Thereafter, the EEG spectrum estimate is processed at step 120 to compute a parameter indicative of the state of activity of the brain. As noted above, it is presently deemed preferable to use a computation of entropy for this purpose. However, other quantifications such as fractal spectrum analysis, Lempel-Ziv complexity, or bispectral or multispectral analyses, such as the bispectral index (BIS), can be used for this

purpose. The result of this computation is the provision of an indication of the state of activity of the brain at step 122.

As noted above, in order to obtain a good estimate of this activity by the mathematical analyses described herein, the length of the signal used for computations has to be sufficient. In practice, the lowest frequency of the band sets the lower limit for the signal length. In the case of the EEG indication generated at step 120, the lower limit for the signal is approximately 60 seconds. This means the indication can only be completely updated by repeating steps 100, 110, 120, and 122 every 60 seconds and sets a lower limit to the response time of the EEG indication for assessing the patient's cerebral state.

A power spectrum of the EMG signal is obtained in step 124, as by obtaining an amplitude spectrum and thereafter squaring the values of the amplitude spectrum to create a power spectrum. The EMG power spectrum provides an indication of EMG activity in step 126.

~~Due to the high frequency range of the EMG activity, for example, above 30 Hz, a comparatively small time window, for example 0.5 seconds, is sufficient to compute the EMG amplitude. This means that changes in the EMG activity can be detected and the indicator updated by repeating steps 100, 110, 124, and 126 substantially faster than changes in the EEG indicator, as shown graphically at steps 124, 124a, 124b, etc.~~

In the example used above, the EMG indicator can be completely updated at a repetition rate of every 0.5 seconds. For simplicity in data processing, the EEG indication will typically also be recomputed every 0.5 seconds. However, since the EEG indicator requires 60 seconds of data, each computation 120, 120a, 120b, etc. will use 59.5 seconds of old EEG signal data and 0.5 seconds of new EEG signal data. Thus, the changes in the cerebral state of the patient contained in the EEG signal data will be reflected only more slowly in the indication produced in steps 120 and 122 than the changes contained in the EMG indication.

The EEG indicator and the EMG indicator are combined in a diagnostic indicator or index in step 128.

The indicators produced in steps 120, 122, 124, 126 and 128 may be

subjected to statistical treatment, such as averaging, if desired.

The combined indication provided by the diagnostic index of step 128 thus provides both reliable information of the activity state of the brain, such as the level of hypnosis or depth of anesthesia as directly found in the EEG signal data, while full  
5 advantage can be taken of the rapidly obtainable information included in the EMG component of the signal which is a more indirect indication of the cerebral state of the patient but is particularly useful in alerting the anesthesiologist to the emergence of a patient from anesthesia.

The components of the diagnostic indicator or index described above are  
10 shown in Fig. 7. An anesthetic agent is administered as a bolus at time zero. The patient enters unconsciousness, as shown by an OAAS level below line 10 in Fig. 7a, thereafter emerges for a short period of time, responsive to stimulation or the lack of further anesthetic agents, and is thereafter rendered unconscious. Fig. 7b shows the entropy indication as obtained from steps 120 and 122 of Fig. 6. Fig. 7c shows the EMG  
15 amplitude obtained from steps 126 and 128 as a root-mean-squared sum over the EMG range of the Fourier spectrum. Data for five seconds are shown as the jagged lines. The smoother lines indicate one minute median filtered values.

The graph of entropy as it relates to the hypnotic state of the patient resembles that of Figs. 2 and 4. With respect to the EMG activity, during the first two  
20 minutes following time zero, there is considerable EMG activity indicating that the patient is awake. Thereafter, the EMG activity decreases as the patient becomes unconscious. The unequivocal and immediate indication that the patient has regained consciousness at the ten minute point given by the EMG amplitude is clearly apparent from Fig. 7c and will be reflected in the diagnostic indicator provided in step 128. This will advise the  
25 anesthesiologist that the patient is emerging from the anesthesia.

In another embodiment of the invention, incorporation of EMG signal data into a diagnostic indicator or index can be obtained by widening the frequency range of spectral entropy computations to one which extends from the EEG range into the EMG range thereby to include both EEG and EMG signal data. Although some small amount  
30 of EMG activity starts from frequencies of 1 Hz or lower, most EMG activity is traditionally quantified in a higher frequency range, such as the range from 40 Hz to 300

Hz (with notch filters at multiples of 50 Hz / 60 Hz in order to filter out the power line interference). However, there exists no clear frequency boundary for the EEG and EMG data signals and an intermediate frequency range between 30 Hz and 50 Hz contains both EEG and EMG components overlapping each other.

5 In providing an entropy based indicator obtained from a frequency range containing both EEG and EMG spectra, it is to be appreciated that this represents a departure from the customary expression of, particularly, EMG signal data. That is, as noted above in connection with the first embodiment of the present invention, EMG signal characteristics are customarily expressed as a voltage amplitude, for example as a  
10 root mean squared spectral amplitude, and the amplitude of the voltage will vary as a result of variations in the EMG signal data. By contrast, EEG entropy is a dimensionless quantity which describes the amount of disorder in the signal. When viewed from the entropic standpoint, the effect of EMG activity on the EEG signal is to create high frequency noise which increases the entropy of the combined signal .

~~15 Entropy varies from 0 to 1, and the values are independent of the amplitude of the signal.~~  
The entropic expression of EEG signal data and the amplitude expression of the EMG signal data thus present a formal incompatibility which is overcome in the present invention by the use of entropy as a characteristics of both signal data.

Further, this embodiment of the invention represents a departure from the  
20 previous entropic treatment of EEG signal data which has been limited to the frequency range in which EEG predominates as compared with EMG. These frequency ranges are, for example, frequencies of 25 Hz and below (see Rezek et al.) or 32 Hz or below (see Bruhn et al.). The present invention contemplates the use of frequencies in a range extending from some lower frequency, for example 0.5 Hz, to a higher frequency which  
25 is in excess of 32 Hz.

The second embodiment of the invention is explained using a frequency range of 0.5 Hz to about 150 Hz. It is deemed preferable to divide the extended frequency range into three-bands: a 0.5 – 47 Hz band; a 63 – 97 Hz band; and a 123 – 147 Hz band. The range is divided into the three bands at these frequencies in order to  
30 avoid the power line harmonics at 50/100 Hz or 60/120 Hz depending on the frequency of the alternating current power mains. The lowest band contains most of the EEG

components, while the two upper bands include primarily EMG activity.

Fig. 8 is a flow chart showing the steps of producing an improved diagnostic indication or index using a widened frequency range for the computation of spectral entropy in accordance with the second embodiment of the present invention. In step 200, the signal data corresponding to the biopotential signals appearing in the electrodes placed on the scalp of the patient is obtained. In step 210, the signal data is subjected to spectral decomposition, as by using Fourier transformation. As noted above, the spectral decomposition may be carried over a frequency range encompassing both the EEG signal data and the EMG signal data, for example, approximately 0.5 Hz to approximately 150 Hz. Also as noted above, the data is divided in spectral bands in order to omit frequencies at those of the power mains.

At step 212, the lower frequency band of the EEG-EMG spectral range as well as the higher frequency bands are processed to compute a measure, such as spectral entropy, indicative of the complexity of the EEG and EMG signal data and state of activity of the brain and the frontal muscles. A combined indicator or index is provided at step 214. As described above in connection with Fig. 6, because the EMG signal data is available for complete updating more frequently than the EEG signal data, updating the combined indicator at the repetition rate by which the EMG signal data parameter can be updated provides a rapid indication to the anesthesiologist of any changes in the hypnotic state of the patient.

Variations of the signal amplitude due to variations in the electrode contact properties etc. affect the EEG and EMG signal data in the same proportion to each other, so the combined EEG-EMG entropy indicator is not affected by the signal amplitude.

Also, the approach taken in the second embodiment of the invention is consistent with the fact that the EEG and EMG frequency bands are overlapping. Thus no artificial boundary for EEG and EMG regions has to be defined since all frequency components are treated in the same way, i.e., a determination of the complexity properties. However, while the present invention features the use of a single algorithm for the range of conscious states of a patient, it will be appreciated the changes to the algorithm may be required, based on signal to noise consideration.

A parameter containing only EEG entropic data from the low frequency



band may be used as a separate indicator as shown in steps 216 and 218. This can be used in connection with the EEG-EMG entropic indication to allow the anesthesiologist to determine what portion of the EEG-EMG entropic indicator comes from brain activity and what portion comes from muscle activity. Thus while a clinical anesthesiologist will probably find the combined EEG-EMG entropic indicator to be highly useful, a researcher may well find a comparison of EEG signal data entropy and the combined EEG-EMG entropy obtained over the wide frequency range to be of interest.

Similarly, a parameter containing the EMG entropic data from the higher frequency bands may be used as a separate parameter by computing the entropy at step 220 and providing the indicator at step 222. The various diagnostic indicators are collectively shown at step 224 in Fig. 8.

While both embodiments of the invention have been described above as utilizing Fourier transformation to decompose the spectrum of signals contained in the electrode biopotentials, other transformations, such as various wavelet transformations, may be employed. In order to obtain the corresponding indicators for pure EEG entropy, EEG-EMG entropy, and/or EMG entropy, the basis functions are divided into two classes, one including the basis functions for EEG activity, and the other including the basis functions for EMG activity. After this classification, the indices for pure EEG entropy and EEG-EMG entropy are computed as described above. It is plausible that for better separation of the EEG and EMG components, a set of basis functions including wavelets emulating the shapes of the EMG spikes may extract the EMG component more effectively.

Fig. 9 illustrates, as a function of time, the behavior of a pure EEG entropy parameter and the combined EEG-EMG entropy parameter along with the depth of anesthesia, as evaluated by an anesthesiologist on an OAAS scale. Also shown is EMG signal data as conventionally expressed as root mean squared spectral amplitude. The jagged lines show values computed from 5 seconds of data, while the smoother lines show one-minute median filtered values. An anesthetic agent is administered as a bolus at time zero.

During the first two minutes, during which time the patient is awake, there is a lot of EMG activity present as can be seen from the graph of Fig. 9d showing EMG

amplitude. As a result of the high EMG activity, the combined EEG-EMG entropy shown in Fig. 9b also shows relatively high values, confirming that the patient is awake.

At about the two minute point the patient loses consciousness as shown in Fig 9a when the OAAS score falls below line 10. Simultaneously, the EMG activity largely disappears as shown in Fig. 9d. The EEG-EMG entropy indicator and the EEG entropy indicator, produced at steps 218 and 226, respectively, of Fig. 8 follow each other down below line 40 demarcating the transition to unconsciousness indicating deepening hypnosis. See Figs. 9b and 9c.

At about 6-7 minutes both the entropy values of Figs. 9b and 9c show that anesthesia starts to lighten. This is because no further hypnotics have been administered. At about ten minutes, the patient wakes up and significant EMG activity again emerges. The pure EEG entropy indicator shown in Fig. 9c predicts and indicates the recovery, but the EMG effect in the combined EEG-EMG entropy indicator shown in Fig 9b makes this more apparent in its crossing of line 40.

Thereafter following the ten minute point, patient is subsequently anesthetized again. The EMG activity gradually disappears as shown in Fig. 9d and EMG-EEG entropy indicator reduces to a pure EEG entropy indicator, as can be seen by a comparison of Figs. 9b and 9c.

It is advantageous to scale the EEG-entropy parameter obtained in step 226 of Fig. 8 and the EEG-EMG entropy parameter obtained in step 218 in such a way that they coincide exactly when the EMG activity ceases completely, as this scaling allows for simultaneous graphical representation of the two pieces of information. This can be done in the following way. Take the frequency range 0.5 to 32 Hz containing mainly EEG signal data to be frequency range  $R_1$ . Take the frequency range 32 to 147 Hz, with the power line frequencies removed, to be frequency range  $R_2$  for mainly EMG signal data.

Perform for the frequency ranges  $[R_1] = [\text{EEG}]$  and  $[R_1] + [R_2] = [\text{EEG}] + [\text{EMG}]$  the steps 1-3 of the Rezek algorithm (Eqs. (1)-(3)) to obtain

$$S[R_1] = \sum_{R_1} P_n(f_i) \log\left(\frac{1}{P_n(f_i)}\right) \quad (5)$$

and

$$S[R_1 + R_2] = \sum_{R_1+R_2} P_n(f_i) \log\left(\frac{1}{P_n(f_i)}\right) \quad (6)$$

Assume for a moment that  $P_n(f_i) = 0$  for all  $f_i$  within the range  $[R_2]$ . In this case, the normalization constant  $C_n[R_1 + R_2] = C_n[R_1]$  and, consequently, the normalized spectra  $P_n[R_1 + R_2]$  and  $P_n[R_1]$  (step 2) are equal. It follows that the unnormalized spectral entropies give by Eqs. (5) and (6) are equal. If these entropy values are now normalized according to Eq. (4), they will no longer be equal, because the normalization factor  $\log(N[R_1 + R_2])$  is obviously larger than  $\log(N[R_1])$ . This situation can be corrected by redefining the normalized entropy  $S_N[R_1]$  in the following way:

$$S_N[R_1] = \frac{\log(N[R_1])}{\log(N[R_1 + R_2])} \frac{S[R_1]}{\log(N[R_1])} = \frac{S[R_1]}{\log(N[R_1 + R_2])} \quad (7)$$

The normalized entropy  $S_N[R_1 + R_2]$  can be defined as previously stated in Eq. (4):

$$S_N[R_1 + R_2] = \frac{S[R_1 + R_2]}{\log(N[R_1 + R_2])} \quad (8)$$

According to these definitions, the EEG-EMG entropy varies from 0 to 1, whereas the pure EEG entropy varies from 0 to  $\log(N[R_1]) / \log(N[R_1 + R_2]) < 1$ . The two entropy values coincide when there is no EMG activity so that  $P(f_i) = 0$  for all  $f_i$  within the range  $[R_2]$ . When EMG activity is present, EEG-EMG entropy is larger than the pure EEG entropy.

In practice, a digital filter is commonly used in processing the signal data obtained from the patient's biopotentials. Due to the characteristics of such a filter the computed entropy of a completely random signal, i.e. white noise, is usually slightly less than 1. For this reason, the entropies may be multiplied by a constant value so as to maintain the above described normalization.

While the foregoing is described using two frequency ranges,  $R_1$ ,  $R_2$ , it will be appreciated that these ideas can be straightforwardly generalized to the case in

which the number of frequency ranges is larger than two.

Fig. 10 shows the resulting normalized EEG entropy  $S_N[R_1]$  (thick curve) together with the normalized EEG-EMG entropy  $S_N[R_1 + R_2]$  (thin curve). When presented in this manner, the EEG entropy gives reliable information of the trend behavior of the patient's brain activity, while the EEG-EMG entropy responds rapidly to fast changes.

Instead of the EEG entropy indicator and the EEG-EMG entropy indicator shown in Fig. 9, it is possible to compute the corresponding entropy indicator for EMG activity alone as shown in Fig 8, steps 220, 222, and to use this together with the pure EEG entropy indicator obtained in steps 216, 218. However, some care must be taken with respect to this approach. When EMG activity ceases due to relaxation of the muscles, some noise is left in the EMG range of the spectrum. The entropy of the noise may be relatively high and give a falsely high value for the level of EMG activity. Therefore, when EMG activity is considered separately and the concept of entropy is used for computations, a noise level should be established below which the EMG signal is considered to be zero.

Apparatus for carrying out the present invention is shown in Fig.11. Electrodes 300 are applied to the head of the patient in a desired manner. Preferably, at least some of the electrodes are applied to the forehead of the patient. At least one pair and usually a plurality of pairs of electrodes are utilized. The biopotentials appearing in the electrodes are received in conductors 302 and are collected into patient cable 304.

Cable 304 connects conductors 302 to protection circuit 306 which is operative in the event the patient is subjected to electro-surgery or cardiac defibrillation. Electro-surgery employs alternating current at radio frequencies, typically between 300 and 3000 Hz to cut tissue and cauterize bleeding blood vessels. A defibrillator delivers a short current pulse to arrest arrhythmia in the heart muscle. Either of these occurrences will significantly affect the signals in conductors 302 and, particularly, the EEG portion of the signals is usually rejected for further use in determining the cerebral state of the patient.

The output of protection circuit 306 is amplified by amplifier 308 and subjected to analog to digital conversion in analog/digital converter 310. Thereafter the

signals are provided to bandpass filter at filter 312 that removes noise and line frequency harmonics from the signals. The output from bandpass filter 312 is connected to artifact detector 314.

5       Artifact detector 314 detects artifacts arising from electrocardiac activity, and other sources. The output of artifact detector 314 is connected to computational unit 316 which carries out the steps of the methods described above and shown in Figs. 6 and 8 and produces an output of the type shown in Figs. 3, 4, 5, 7, 9, and 10 in display 318. Or, the information may be presented in display 318 in numerical form. Display 318 may also display other physiological data, such as electrocardiographic data, breath rate,  
10       pulse, blood pressure, etc., obtained from other monitors.

      Also, while artifact detector 314 is used to remove artifacts, the presence of artifacts can also be dealt with in the signal processing occurring in computational unit 316. For example, eye movements have been found to create simultaneous spikes in both the lower frequency EEG signal data as well as in the higher frequency EMG signal  
15       data. Sensing of the presence simultaneous spikes in both these frequency bands may be deemed to result from eye movements and particularly EEG signal data containing such artifacts can be eliminated from use in making the determination of the cerebral state of the patient. The same is also true when excessive muscular activity and corresponding large EMG signal data is present.

20       The invention has been described above in connection with cerebral states induced by the administration of an anesthetic agent. However, it will be appreciated that the method and apparatus may be used in connection with other physiological conditions which are reflected in EEG and EMG signal data obtained from a patient and with drugs other than anesthetic agents. It is therefore recognized that other equivalents,  
25       alternatives, and modifications aside from those expressly stated, are possible and within the scope of the appended claims.

## CLAIMS

1. A method for ascertaining the cerebral state of a patient, including a state resulting from the administration of a drug, said method comprising the steps of :

- (a) obtaining EEG signal data from the patient;
- (b) obtaining EMG signal data from the patient;
- 5 (c) analyzing a sample of sequential EEG signal data to obtain a first indication indicative of the cerebral state of the patient;
- (d) analyzing a sample of sequential EMG signal data temporally related to the EEG signal data sample to obtain a second indication indicative of electromyographic activity in the patient; and
- 10 (e) producing a composite indication from the first and second indications obtained at steps (c) and (d) indicative of the cerebral state of the patient.

2. A method for ascertaining the cerebral state of a patient, including a state resulting from the administration of a drug, said method rapidly indicating changes in such state and comprising the steps of :

- (a) obtaining EEG signal data from the patient;
- 5 (b) obtaining EMG signal data from the patient, the EMG signal data being primarily of a higher frequency than the EEG signal data which is primarily of lower frequency;
- (c) analyzing a sample of sequential EEG signal data to obtain a first indication indicative of the cerebral state of the patient, the length of a EEG signal data
- 10 sample being such as to provide an cerebral state indication of desired accuracy;
- (d) analyzing a sample of sequential EMG signal data temporally related to the EEG signal data sample to obtain a second indication indicative of electromyographic activity in the patient, it being possible to use a EMG signal data sample of shorter length than that of the EEG signal data sample due to the higher
- 15 frequency of the EMG signal data; and
- (e) producing a composite indication of the cerebral state of the patient from the first and second indications obtained at steps (c) and (d) indicative of the cerebral state of the patient, which composite indication can be updated at a repetition

rate determined by the shorter sample length of the EMG signal data to rapidly indicate  
20 changes in the cerebral state of the patient.

3. The method according to claim 1 or claim 2 wherein step (c) is further defined as obtaining a measure of the complexity of the EEG signal data as the first indication.

4. The method according to claim 3 wherein step (c) is further defined as obtaining a measure of the entropy of the EEG signal data as the first indication.

5. The method according to claim 4 wherein step (c) is further defined as obtaining the spectral entropy of the EEG signal data as the first indication.

6. The method according to claim 4 wherein step (c) is further defined as obtaining the approximate entropy of the EEG signal as the first indication.

7. The method according to claim 3 wherein step (c) is further defined as obtaining a Lempel-Ziv complexity measure of the EEG signal data as the first indication.

8. A method according to claim 3 wherein step (c) is further defined as obtaining the first indication from fractal spectrum analysis.

9. The method according to claim 1 or claim 2 wherein step (c) is further defined as obtaining the first indication from higher order frequency domain analysis including the bispectrum or trispectrum.

10. The method according to claims 1, 2 or 3 wherein step (c) is further defined as obtaining the first indication from frequency domain power spectral analysis of the EEG signal data.

11. The method according to claim 1 or claim 2 wherein step (c) is further defined as obtaining the first indication from a combination of analytical quantities obtained from the EEG signal data.

12. The method according to claim 11 wherein step (c) is further defined as employing a bispectral index (BIS) of the EEG signal data as the first indication.

13. The method according to claim 1 or claim 2 wherein prior to analyzing the samples in steps (c) and (d) the EEG and EMG signal data is subjected to spectral decomposition.

14. The method according to claim 13 further defined as carrying out the spectral decomposition by means of a Fourier transform.

15. The method according to claim 13 further defined as carrying out the spectral decomposition by employing a set of basis functions other than a Fourier set of functions.

16. The method according to claim 15 further defined as carrying out the spectral decomposition by employing a set of basic functions corresponding to wavelet transformation.

17. The method according to claims 1, 2 or 3 wherein step (d) is further defined as obtaining the second indication from a frequency domain power spectrum of the EMG signal data.

18. The method according to claim 3 wherein step (d) is further defined as obtaining a measure of the complexity of the EMG signal data as the second indication.



19. The method according to claim 18 wherein in step (d) a noise level is established below which the EMG signal data is considered to be zero.

20. The method according to claim 1 or claim 2 further defined as repeating steps (c), (d), and (e) to update the composite indication.

21. The method according to claims 1, 2, 3, 4, or 5 further defined as one for ascertaining the hypnotic state of a patient.

22. The method according to claims 17 further defined as one for ascertaining the hypnotic state of a patient.

23. The method according to claim 21 further defined as repeating steps (c), (d), and (e) to update the composite indication.

24. The method according to claim 17 further defined as repeating steps (c), (d), and (e) to update the composite indication.

25. A method for ascertaining the cerebral state of a patient, including a state resulting from the administration of a drug, said method comprising the steps of:

5 (a) obtaining biopotential signals from the patient, the biopotential signals containing EEG signal data and EMG signal data, the EMG signal data being primarily of a higher frequency than the EEG signal data which is primarily of a lower frequency;

(b) analyzing a sample of sequential signal data over a frequency range that is sufficiently wide to include both the EEG and EMG signal data to obtain a measure of the complexity of the signal data; and

10 (c) providing the measure as an indication of the cerebral state of the patient.

26. A method for ascertaining the cerebral state of a patient, including a

state resulting from the administration of a drug, said method rapidly indicating changes in such state and comprising the steps of:

- 5 (a) obtaining biopotential signals from the patient, the biopotential signals containing EEG signal data and EMG signal data, the EMG signal data being primarily of a higher frequency than the EEG signal data which is primarily of lower frequency;
- 10 (b) analyzing a sample of sequential signal data over a frequency range that is sufficiently wide to include both the EEG and EMG signal data to obtain a measure of the complexity of the signal data, it being possible to use a EMG signal data sample of shorter length than that of the EEG signal data sample due to the higher frequency of the EMG signal data; and
- 15 (c) providing the measure as an indication of the cerebral state of the patient, which indication can be updated at a repetition rate determined by the shorter sample length of the EMG signal data to rapidly indicate changes in the cerebral state of the patient.

27. The method according to claim 25 or claim 26 wherein step (b) is further defined as analyzing the biopotential signals over a frequency range extending from a frequency of about 0.5 Hz to a frequency which is above 32 Hz.

28. The method according to claim 25 or claim 26 wherein step (b) is further defined as obtaining a measure of the entropy of the signal data.

29. The method according to claim 27 wherein step (b) is further defined as obtaining a measure of the entropy of the signal data.

30. The method according to claim 28 wherein step (b) is further defined as obtaining the spectral entropy of the signal data.

31. The method according to claim 28 wherein step (b) is further defined as obtaining the approximate entropy of the signal data.

32. The method according to claim 25 or claim 26 wherein step (b) is further defined as obtaining a Lempel-Ziv complexity measure of the signal data.

33. A method according to claim 25 or claim 26 wherein step (b) is further defined as obtaining the complexity measure from fractal spectrum analysis.

34. The method according to claim 25 or claim 26 wherein prior to analyzing the sample in step (b) the biopotential signal is subjected to spectral decomposition.

35. The method according to claim 34 further defined as carrying out the spectral decomposition by means of a Fourier transform.

36. The method according to claim 34 further defined as carrying out the spectral decomposition by employing a set of basis functions other than a Fourier set of functions.

37. The method according to claim 36 further defined as carrying out the spectral decomposition by employing a set of basic functions corresponding to wavelet transformation.

38. The method according to claim 25 or claim 26 further defined as repeating steps (c), (d), and (e) to update the indication.

39. The method according to claim 25 or claim 26 further defined as one for ascertaining the hypnotic state of a patient.

40. The method according to claim 27 further defined as one for ascertaining the hypnotic state of a patient.

41. The method according to claim 28 further defined as one for ascertaining the hypnotic state of a patient.

42. The method according to claim 29 further defined as one for ascertaining the hypnotic state of a patient.

43. The method according to claim 39 further defined as repeating steps (c), (d), and (e) to update the composite indication.

44. The method according to claim 25 or claim 26 further defined as including the steps of analyzing a sample of the EEG signal data to obtain a complexity measure of the EEG signal data and providing the complexity measure of the EEG signal data as a further indication of the cerebral state of the patient.

45. The method according to claim 44 further defined as normalizing the further indication obtained from the analysis of the EEG signal data and the EEG-EMG signal data indication so that the further indication and EEG-EMG indication are equal in the absence of EMG signal data.

46. The method according to claim 45 wherein the normalizing is carried out by multiplying the complexity measure of the EEG signal data by a quantity comprising the logarithm of the number of frequency components used for computations for the EEG signal data complexity measure divided by the logarithm of the number of  
5 frequency components used for the computations for the combined EEG-EMG complexity measure.

47. The method according to claim 45 further defined as applying a constant to the normalized indications to maintain the normalization.

48. The method according to claim 1 or claim 2 wherein step (a) is further defined as obtaining the EEG signal data in a frequency range of approximately

49. The method according to claim 1 or claim 2 wherein step (b) is further defined as obtaining EMG signal data in a range of approximately 32 - 300 Hz.

50. The method according to claim 49 further defined as notch filtering the EMG signal data to remove power line frequency harmonics.

51. The method according to claim 25 or claim 26 further defined as notch filtering to remove power line frequency harmonics.

52. The method according to claim 1, 2, 25, or 26 wherein the EEG signal data and the EMG signal data are obtained from a common signal source.

---

53. The method according to claim 52 wherein the EEG and EMG signal data are obtained from biopotential electrodes applied to the head of the patient.

54. The method according to claim 53 wherein at least the EMG signal data is obtained from electrodes applied to the forehead of the patient.

55. The method according to claim 1 or claim 2 further defined as processing the EEG and EMG signal data to detect artifacts.

56. The method according to claim 25 or 26 further defined as processing the biopotential signals or signal data to detect artifacts.

57. The method according to claim 55 further defined as filtering the signal data to remove artifacts.

58. The method according to claim 56 further defined as filtering the signal data or biopotential signals to remove artifacts.

59. The method according to claim 55 further defined as preventing the use of signal data affected by artifacts.

60. The method according to claim 56 further defined as preventing the use of signal data or biopotential signals affected by artifacts.

61. The method according to claim 55 further defined as detecting excessive muscle activity in the patient from the EMG signal data and preventing the use of EEG signal data affected by the muscle activity.

62. The method according to claim 56 further defined as detecting excessive muscle activity in the patient from the biopotential signals or signal data and preventing the use of EEG signal data affected by the muscle activity.

63. The method according to claim 55 further defined as including the step of sensing the presence of electrical energy at electro surgical frequencies and as preventing the use of signal data affected by such an artifact.

64. The method according to claim 56 further defined as including the step of sensing the presence of electrical energy at electro surgical frequencies and as preventing the use of biopotential signals or signal data affected by such an artifact.

65. The method according to claim 55 further defined as detecting simultaneous spikes in both the EEG signal data and EMG signal data as eye movement artifacts and preventing the use of signal data affected by such artifacts.

66. The method according to claim 56 further defined as detecting simultaneous spikes in both the EEG signal data and EMG signal data as eye movement artifacts and preventing the use of biopotential signals or signal data affected by such artifacts.

67. A method for ascertaining the depth of anesthesia of a patient, said method rapidly indicating changes in the hypnotic state of the patient and comprising the steps of:

- 5 (a) obtaining biopotential signals from the patient, the biopotential signals containing EEG signal data and EMG signal data, the EMG signal data being primarily of a higher frequency than the EEG signal data which is primarily of lower frequency;
- 10 (b) analyzing a sample of sequential signal data existing in a frequency range extending from a frequency of about 0.5 Hz to a frequency which is above 32 Hz to obtain a measure of the complexity of the signal data, it being possible to use a EMG signal data sample of shorter length than that of the EEG signal data sample due to the higher frequency of the EMG signal data;
- 15 (c) providing the complexity measure as a first indication of the cerebral state of the patient, which indication can be updated at a repetition rate determined by the shorter sample length of the EMG signal data to rapidly indicate changes in the cerebral state of the patient;
- (d) analyzing a sample of EEG signal data to obtain a complexity measure of the EEG signal data;
- 20 (e) providing the complexity measure of the EEG signal data as a second indication of the cerebral state of the patient; and
- (f) normalizing the first indication and second indication so that the first indication and second indication are equal in the absence of EMG signal data.

68. Apparatus for ascertaining the cerebral state of a patient, including a state resulting from the administration of a drug, said apparatus comprising:

- (a) means for obtaining biopotential signals from the patient, the biopotential signals containing EEG signal data and EMG signal data;
- 5 (b) means analyzing a sample of sequential EEG signal data to obtain a first indicator indicative of the cerebral state of the patient and analyzing a sample of sequential EMG signal data temporally related to the EEG signal data sample to obtain a

second indicator indicative of electromyographic activity in the patient; and

- 10 (c) means producing a composite indicator from the first and second indicators indicative of the cerebral state of the patient.

5 69. The apparatus according to claim 68 wherein said analyzing means is further defined as using a length of an EEG signal data sample to determine the first indicator and using an EMG signal data sample of shorter length than the EEG signal data sample to determine said second indicator, said analyzing means completely updating said second indicator more frequently than said first indicator.

70. The apparatus according to claim 68 or claim 69 wherein said analyzing means is further defined as obtaining a measure of the complexity of the EEG signal data as the first indicator.

71. The apparatus according to claim 70 wherein said analyzing means is further defined as obtaining a measure of the entropy of the EEG signal data as the first indicator.

72. The apparatus according to claim 70 wherein said analyzing means is further defined as obtaining a Lempel-Ziv complexity measure of the EEG signal data as the first indicator.

73. The apparatus according to claims 68, 69, or 70 wherein said analyzing means is further defined as obtaining the second indication from a frequency domain power spectrum of the EMG signal data.

74. The apparatus according to claims 68, 69, 70, or 71 further defined as one for ascertaining the hypnotic state of a patient.

75. Apparatus for ascertaining the cerebral state of a patient, including a state resulting from the administration of a drug, said apparatus comprising:



(a) means for obtaining biopotential signals from the patient, the biopotential signals containing EEG signal data and EMG signal data, the EMG signal data being primarily of a higher frequency than the EEG signal data which is primarily of a lower frequency;

(b) means for analyzing a sample of sequential signal data over a frequency range that is sufficiently wide to include both the EEG and EMG signal data to obtain a measure of the complexity of the signal data; and

(c) means providing the complexity measure as an indicator of the cerebral state of the patient.

76. The apparatus according to claim 75 wherein said analyzing means is further defined as using a length of EEG signal data and using a EMG signal data sample of shorter length than the EEG signal data sample, and wherein said means updates said indicator a repetition rate determined by the shorter sample length of the EMG signal data to indicate changes in the cerebral state of the patient.

77. The apparatus according to claim 75 or claim 76 wherein said analyzing means is further defined as analyzing the signal data over a frequency range extending from a frequency of about 0.5 Hz to a frequency which is above 32 Hz.

78. The apparatus according to claim 75 or claim 76 wherein said analyzing means is further defined as obtaining a measure of the entropy of the signal data.

79. The apparatus according to claim 77 wherein said analyzing means is further defined as obtaining a measure of the entropy of the signal data.

80. The apparatus according to claim 75 or claim 76 wherein said analyzing means is further defined as obtaining a Lempel-Ziv complexity measure of the signal data.

81. The apparatus according to claim 75 or claim 76 further defined as one for ascertaining the hypnotic state of a patient.

82. The apparatus according to claim 75 or claim 76 wherein said analyzing means further defined as analyzing a sample of the EEG signal data to obtain a complexity measure of the EEG signal data and said providing means is further defined as providing the complexity measure of the EEG signal data as further indicator  
5 of the cerebral state of the patient.

83. The apparatus according to claim 82 further including means for normalizing the further indication obtained from the analysis of the EEG signal data and the EEG-EMG signal data indication so that the further indication and EEG-EMG indication are equal in the absence of EMG signal data.

84. The apparatus according to claim 68 or claim 75 further defined as including means notch filtering the signal data to remove power line frequency harmonics.

85. The apparatus according to claim 68 or claim 75 further defined as including means for processing the signal data to detect artifacts.

86. The apparatus according to claim 85 further defined as including means for filtering the signal data to remove artifacts.

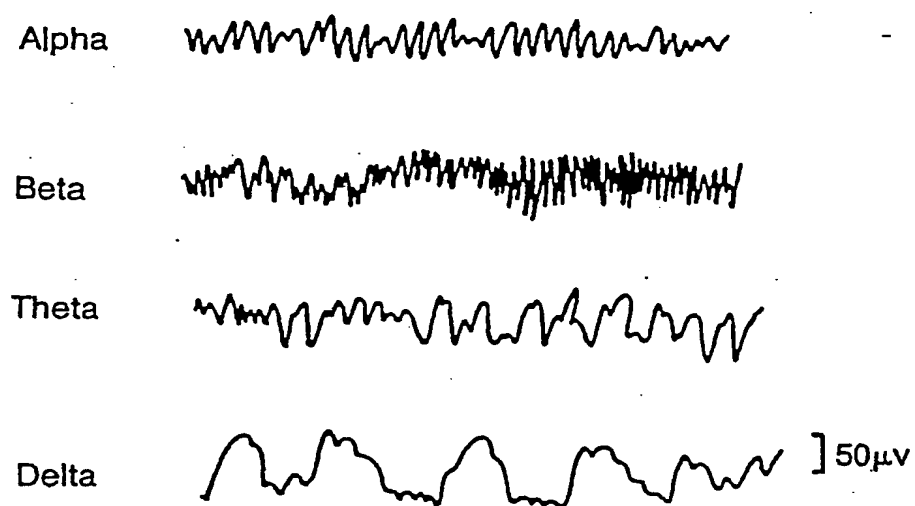


FIG. 1

FIG. 2a

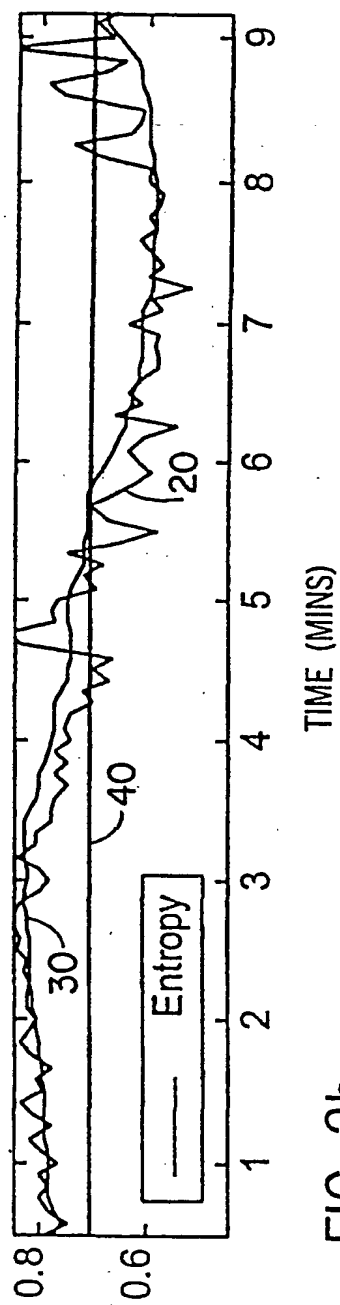
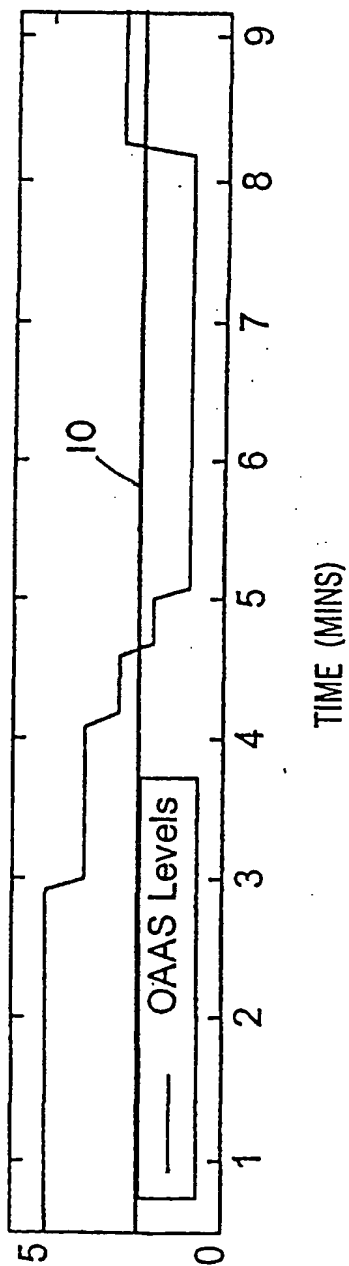


FIG. 2b

FIG. 3a

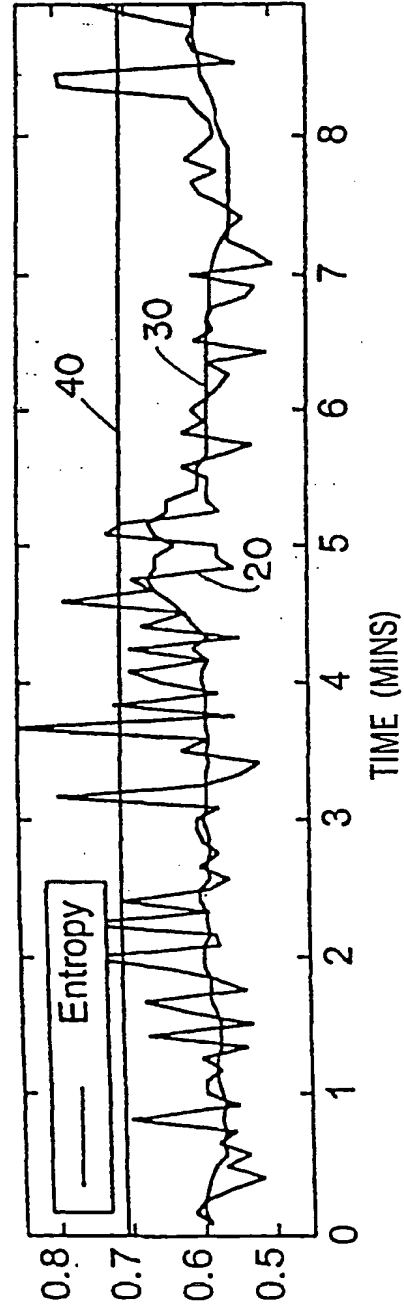
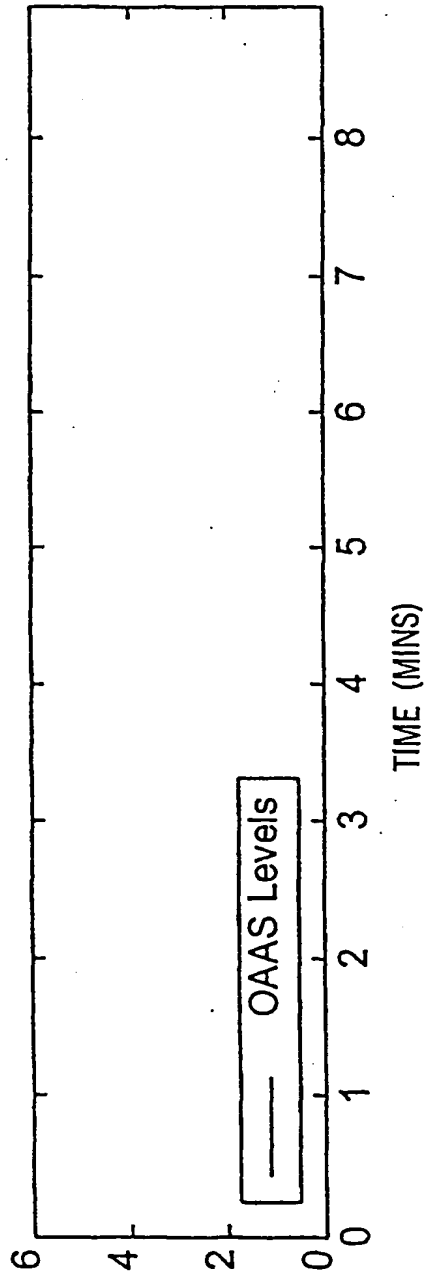


FIG. 3b

FIG. 4a

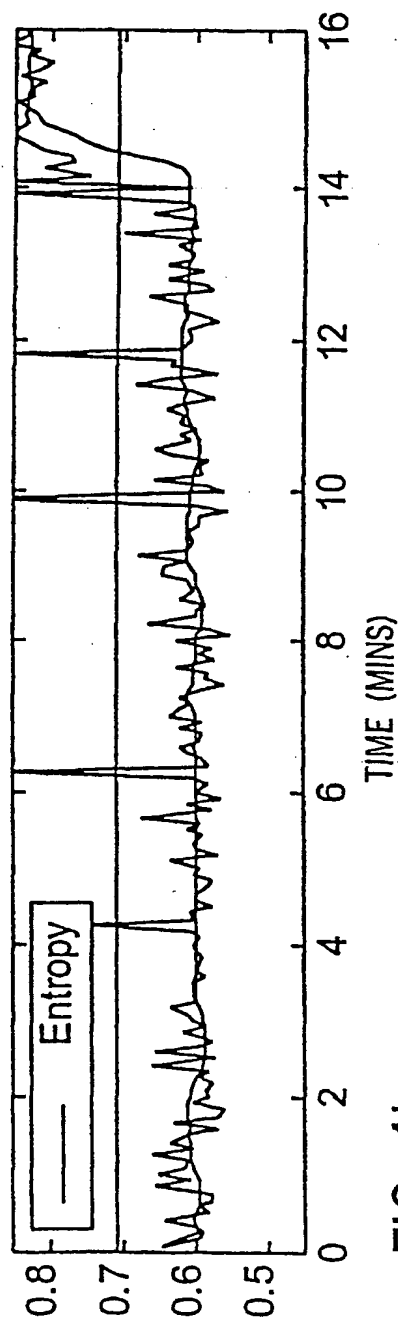
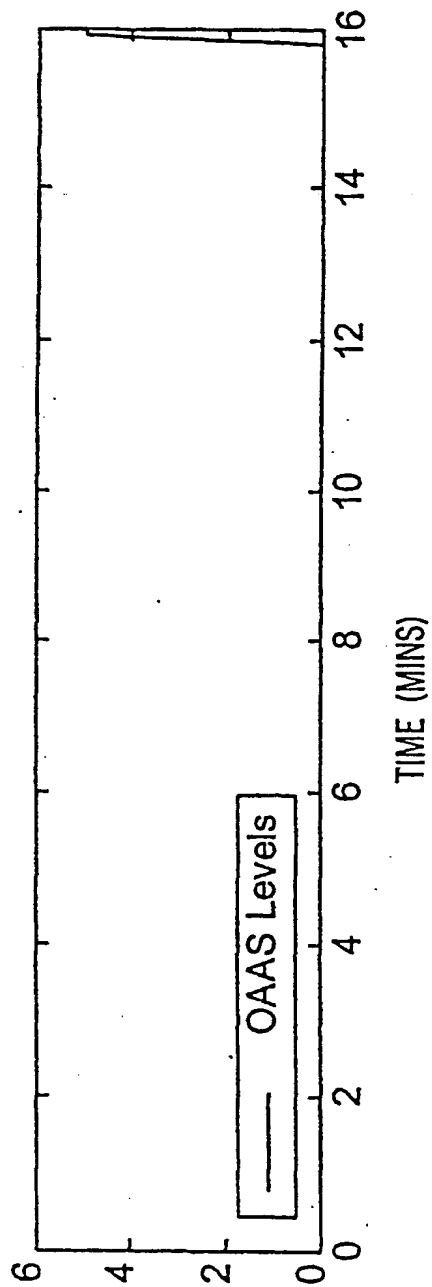


FIG. 4b

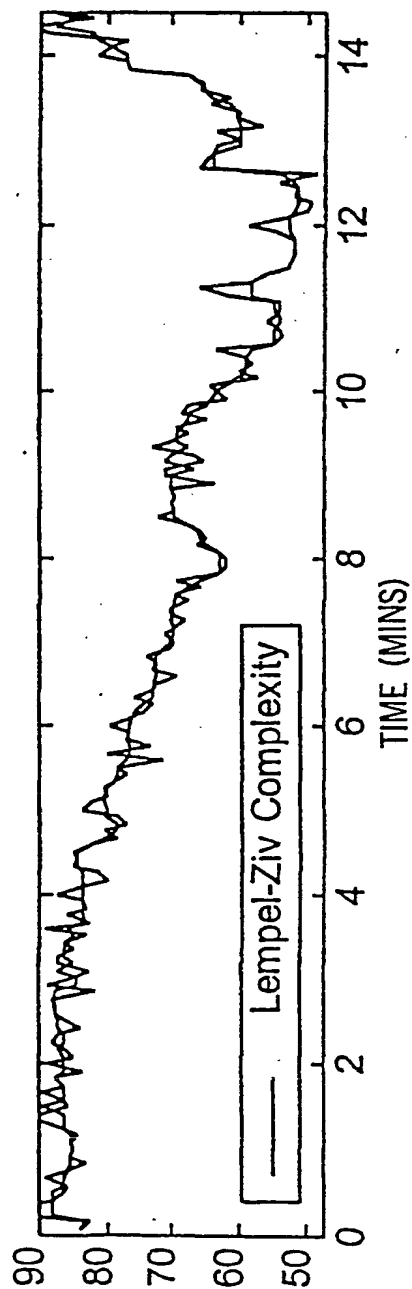
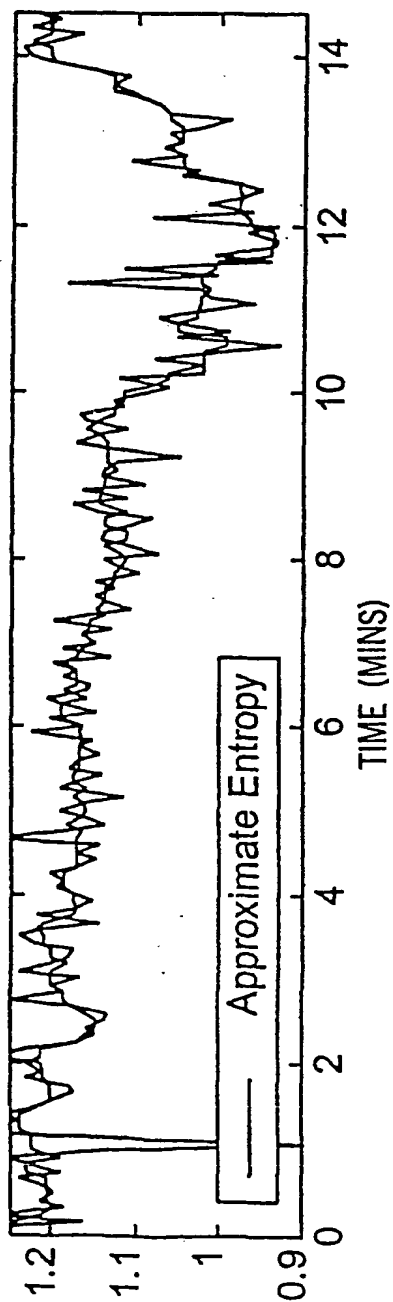
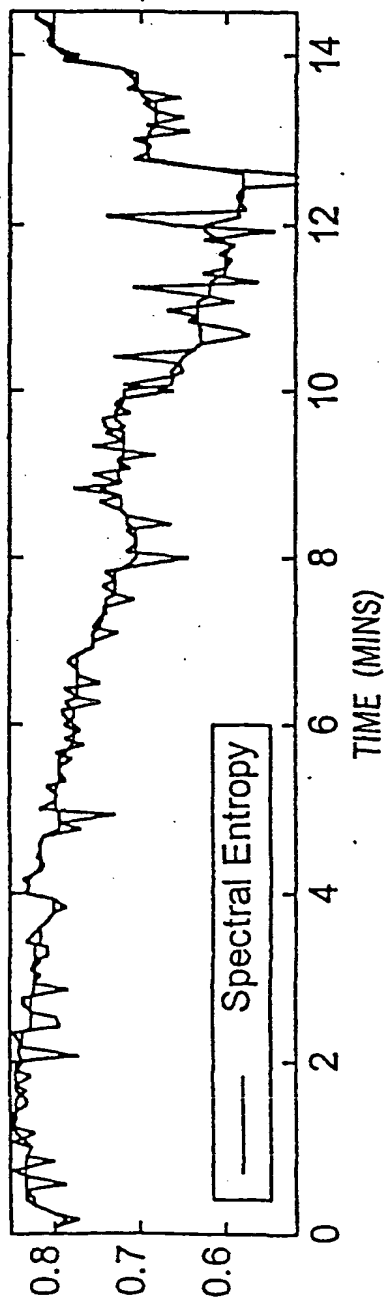


FIG. 6

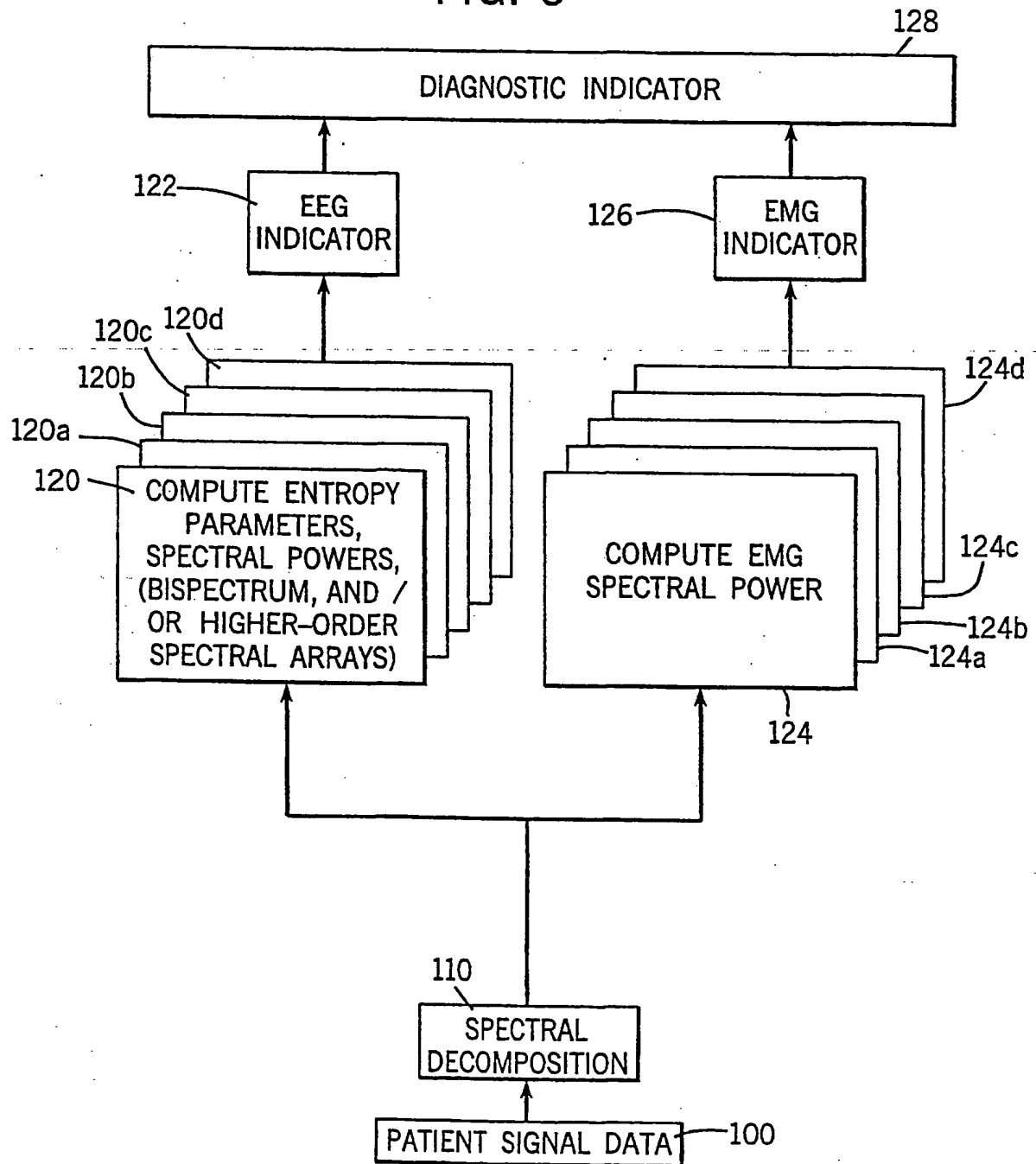




FIG. 7a

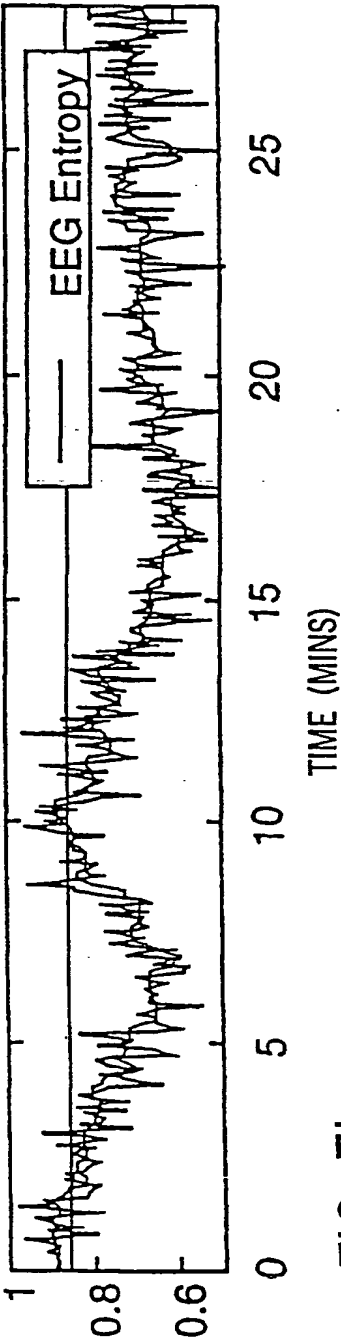
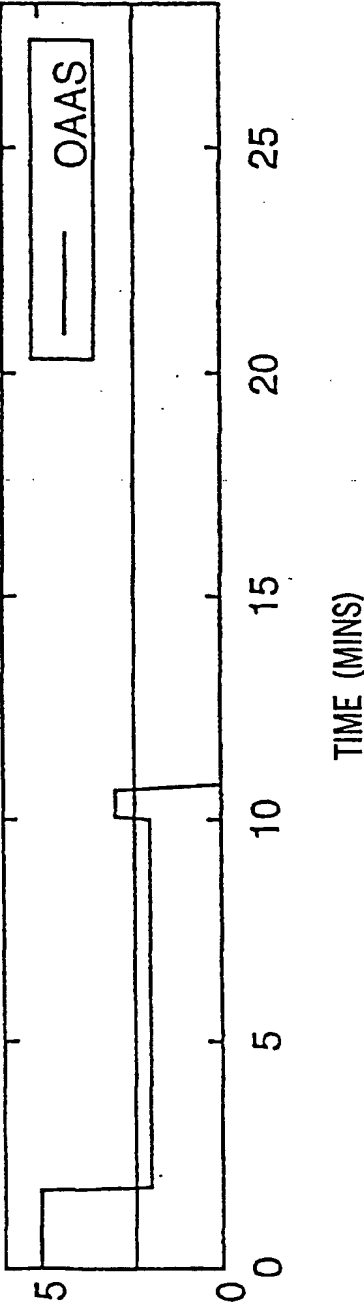


FIG. 7b

8/13

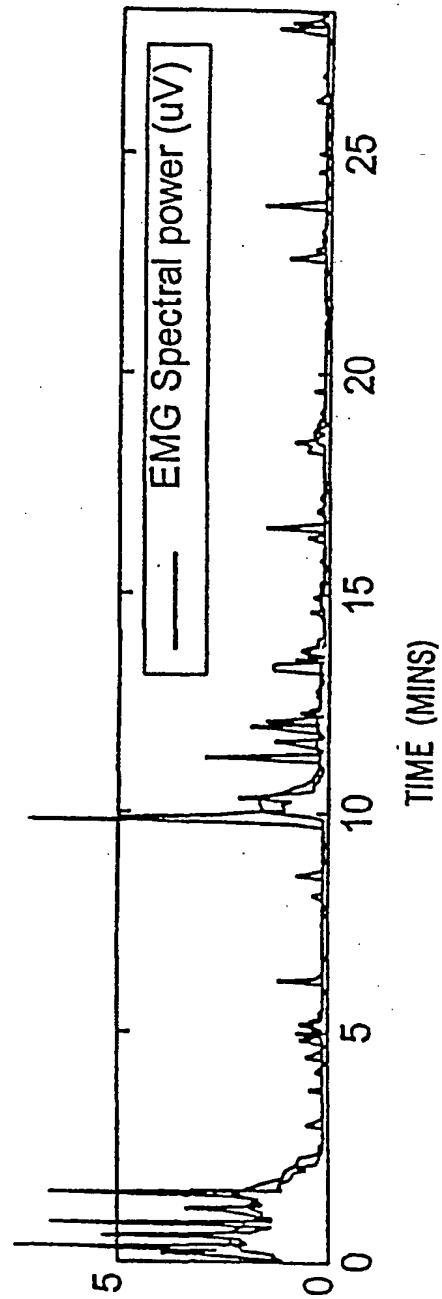


FIG. 7c

9/13

FIG. 8

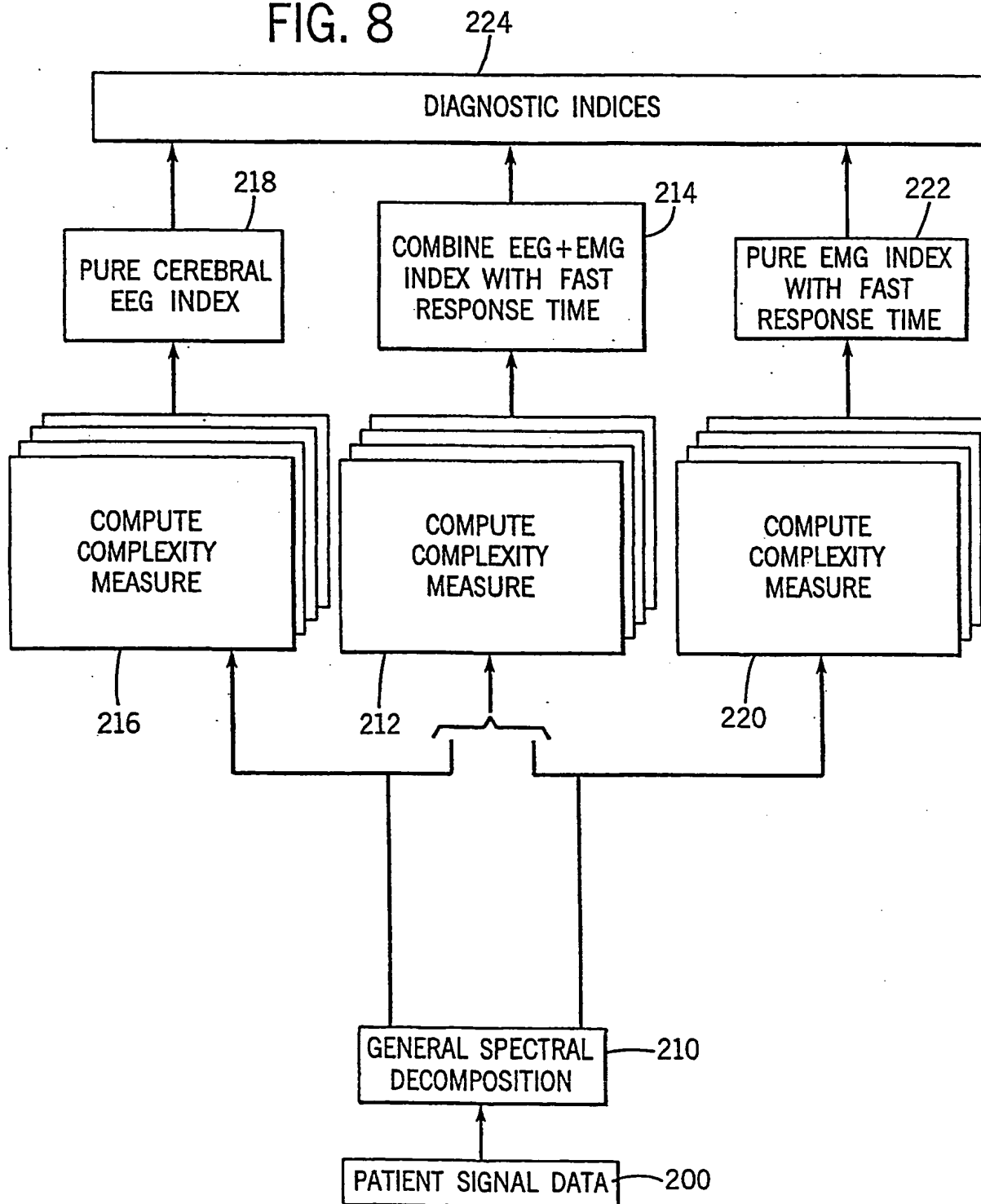


FIG. 9a

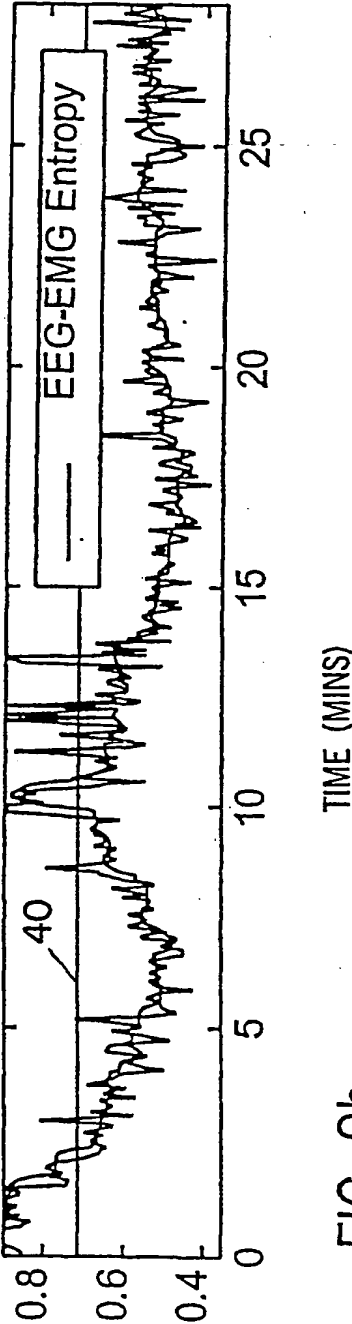
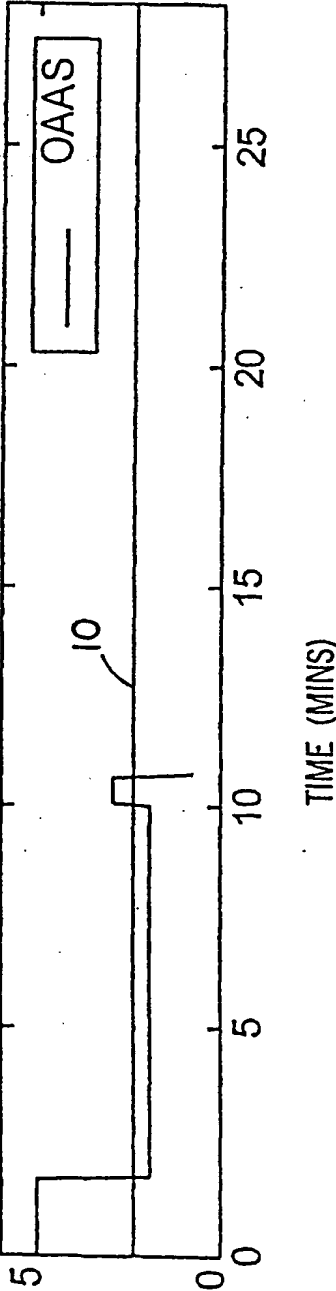


FIG. 9b

FIG. 9c

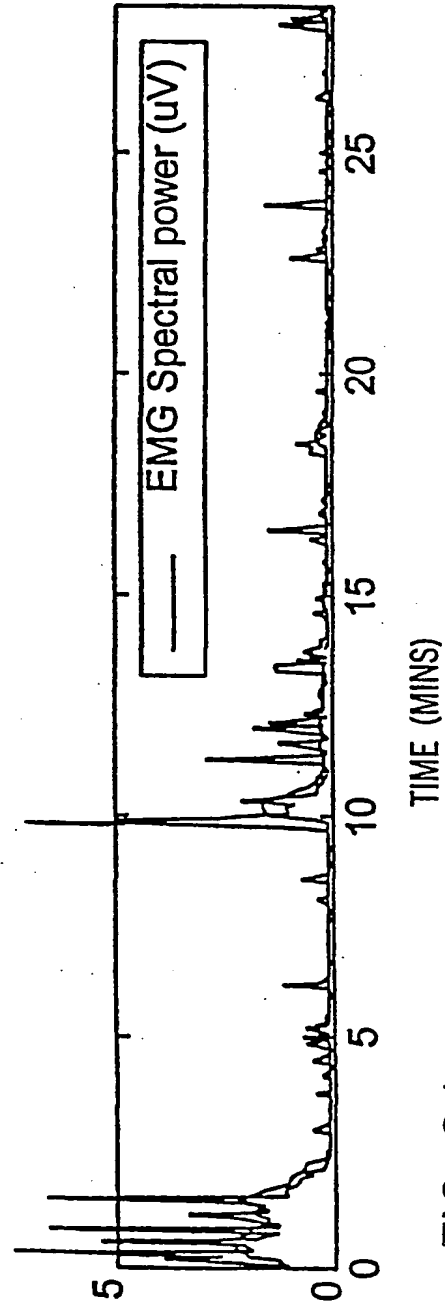
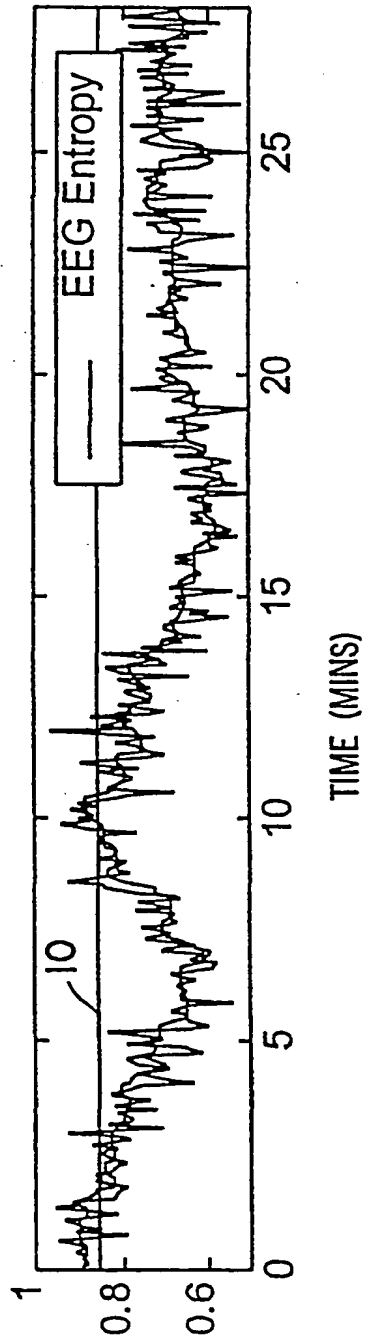
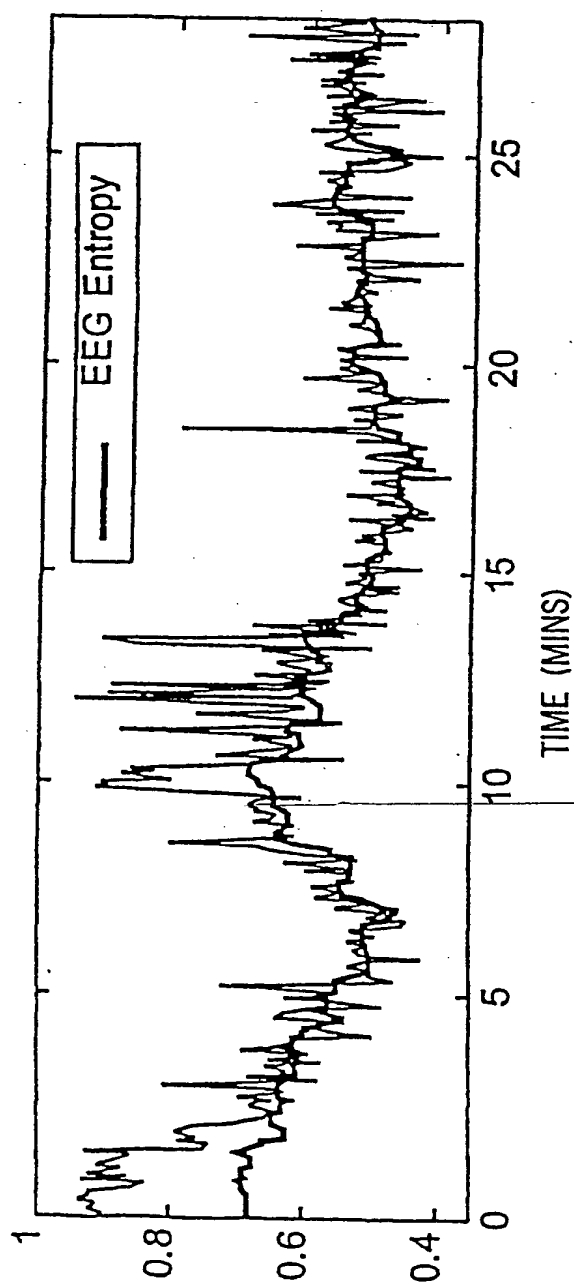


FIG. 9d

12/13

FIG. 10



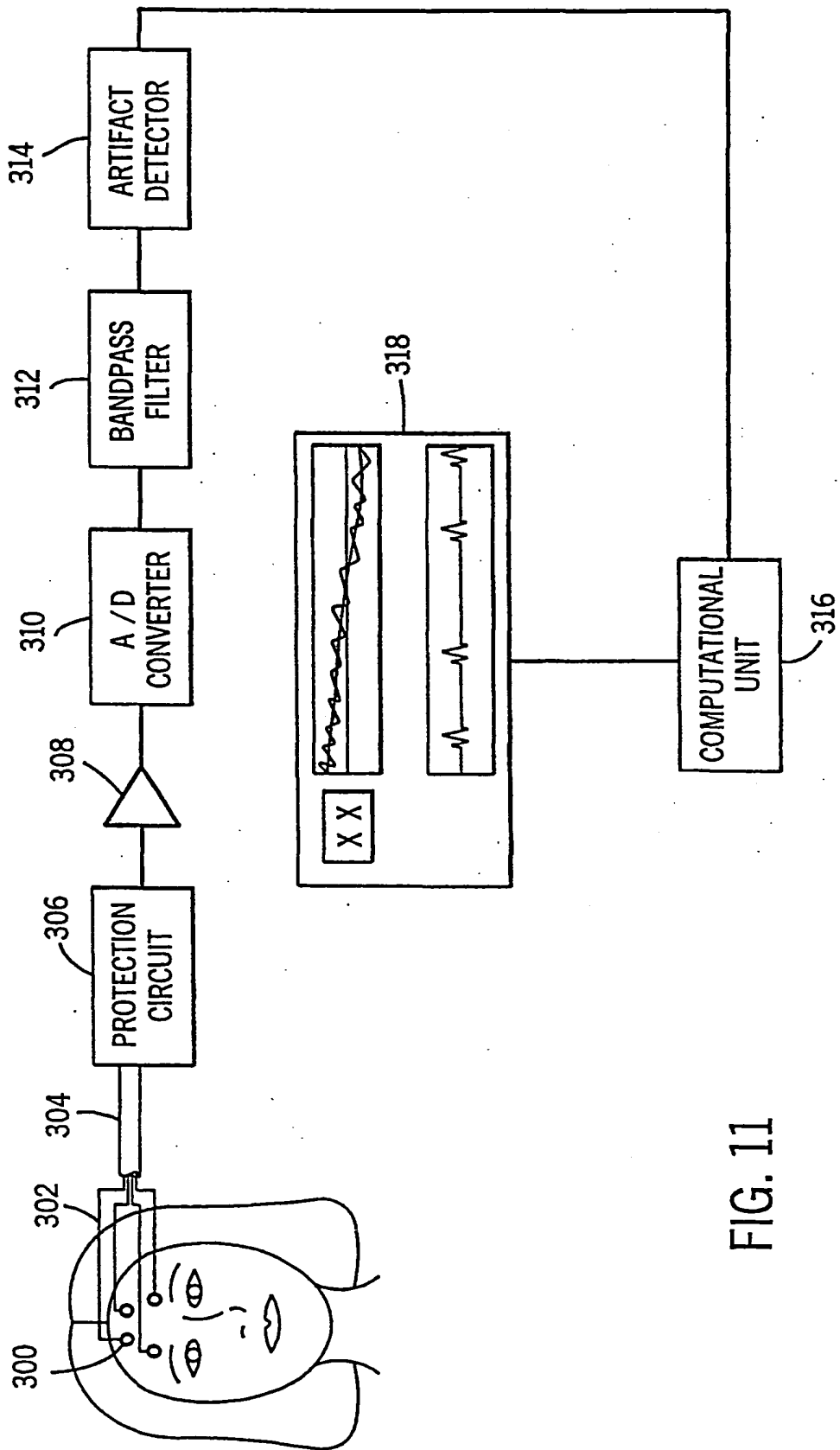


FIG. 11

## INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/IB 01/01932

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61B5/0488 A61B5/0476

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 067 467 A (JOHN ERWIN ROY) 23 May 2000 (2000-05-23) abstract	68,75
A	US 5 320 109 A (SAINI VIKAS ET AL) 14 June 1994 (1994-06-14) cited in the application abstract	68,75
A	WO 91 13584 A (PEARLMAN ANDREW L ;SRD SHORASHIM MEDICAL LTD (IL)) 19 September 1991 (1991-09-19)	

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

1 March 2002

Date of mailing of the international search report

07/03/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Papone, F



## INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat. Application No

PCT/IB 01/01932

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6067467	A	23-05-2000	US 5699808 A	23-12-1997
US 5320109	A	14-06-1994	AT 178198 T	15-04-1999
			DE 69228823 D1	06-05-1999
			DE 69228823 T2	25-11-1999
			EP 0610365 A1	17-08-1994
			EP 0898234 A1	24-02-1999
			JP 7500983 T	02-02-1995
			WO 9307804 A1	29-04-1993
			US 5458117 A	17-10-1995
WO 9113584	A	19-09-1991	CA 2077191 A1	29-08-1991
			EP 0517793 A1	16-12-1992
			WO 9113584 A1	19-09-1991

